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# SENSORY FUNCTIONS OF THE OPTIC THALAMUS OF THE MONKEY (MACACUS RHESUS)

## SYMPTOMATOLOGY AND FUNCTIONAL LOCALIZATION INVESTIGATED WITH THE METHOD OF LOCAL STRYCHNINIZATION

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Local strychninization of those structures of the central nervous system which subserve sensory functions results in marked, typical symptoms of sensory excitation. This has been established in previous experiments for the dorsal gray horns or pillars of the spinal cord and for the sensory cortex. In 1929 and 1930 we applied this method in a study of the sensory functions of the optic thalamus of the cat [1] by injecting a minute quantity of a solution of strychnine into that part of the central nervous system. The present paper deals with a similar investigation of the optic thalamus of the monkey (Macacus rhesus). Here, again, it was found that local strychninization of various parts of the thalamus results in a typical syndrome and that a definite functional localization in this chief subcortical sensory center exists.

### METHODS

The animals were all Macacus rhesus. Fifty-eight monkeys were used, each of which received one injection of strychnine on each side, thus making one hundred and sixteen experiments. Twenty-nine of the injections were inadvertently made outside the thalamus, leaving eighty-seven intrathalamic injections.

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1. Dusser de Barenne, J. G., and Sager, O.: Ztschr. f. d. ges. Neurol. u. Psychiat. **133**:231-272, 1931.

*Anesthesia.*—Divinyl ether [2] was used. The great advantage of this anesthetic, especially in experiments like ours, is the quick recovery; within a few minutes after its administration is stopped the animal is sitting on its feet again and is fully awake.

*Injection of Strychnine.*—The intrathalamic injections were made by a microinjection technic similar to that previously described.[1] A tuberculin syringe containing a 3 per cent solution of strychnine sulfate (colored by toluidine blue) is held in a special holder, the heavy base of which can be clamped rigidly to the operating table. The syringe holder can be screwed forward and backward along a millimeter scale by a rack and pinion; a pointer attached to the holder indicates its position on the millimeter scale. In the other end of the holder, coaxially with the syringe, a micrometer caliper is inserted, the spindle of which presses against the handle of the piston of the syringe. The syringe holder can be adjusted in any desired position and direction in space by three micrometer screws; the deviation of the needle from the horizontal—its inclination in one or the other direction—is measured on a half-circle, graduated in degrees, by a small plummet hanging from the syringe holder.

When the cortex of the animal is exposed, the apparatus for injection is clamped to the operating table alongside the animal and the syringe with its needle brought into the position and direction desired for the injection. Then the holder, carrying the syringe holder and the micrometer caliper, is screwed forward by the rack and pinion until the point of the needle touches the central nervous system at the point of entrance, and a reading of its position is taken on the millimeter scale. Then the holder is screwed forward again by the rack and pinion over the desired distance; thus the needle pierces the nerve tissue, bringing its point into the proper position in the thalamus. Now the holder is screwed back 0.5 mm.; this is done to leave the tip of the needle track "empty" for the injection of from 0.5 to 2 cu. mm. of the strychnine solution. The injection is now effected; the thimble of the micrometer caliper is turned clockwise, which pushes forward its movable spindle and with it the plunger of the syringe, thus expelling the desired minute amount of strychnine solution from the needle.

As in the experiments on the cat's thalamus, it was found in these experiments on the monkey that the strychnine does not remain localized at the end of the needle track but is distributed along its entire length. This, of course, is a complication, which necessitates a greater number of experiments than when superficially located sensory structures are investigated with this method. Fortunately, the thalamus of the monkey is much larger than that of the cat, so that it is much easier, by choosing appropriately the route of injection, to reach individual thalamic nuclei. For the lateral portions of the lateral and lateroventral nuclei the injections were performed in a more or less transverse plane through a trephine hole over the sensorimotor cortex; for the medial portions of these nuclei and for the medial nuclei the injections were made in a sagittal plane or a plane slightly deviating from the sagittal one, either through the frontal lobe or by an occipital approach through a small trephine hole in the planum occipitale and through the cerebellum and brain stem. These various routes will be indicated hereafter as the "transverse," the "sagittofrontal" and the "sagitto-occipital" routes, respectively.

If the injection is made by the transverse route, the needle has to enter the brain at some point of the "sensory" cortex.[3] The symptoms observed after the

2. The divinyl ether was put at our disposal by Merck & Co., Rahway, N. J.
3. Dusser de Barenne, J. G.: Proc. Roy. Soc., London, s.B **96**:272-291, 1924.

intrathalamic injection could then be due, at least in part, to local strychninization of the cortex, where the needle pierced it. To obviate this complication, the site of entrance of the needle on the cortex was always killed by thermocoagulation before the injection was made. In a sagittofrontal or a sagitto-occipital injection the location of the plane of injection with respect to the median plane of the head differed from case to case, depending on the intrathalamic position of the nucleus into which the injection was to be made.

To insure proper location of the intrathalamic injection, it is essential that the head of the monkey be fixed rigidly and with a definite orientation in space. This is accomplished by the use of a special holder for the heads of the smaller monkeys commonly used in the laboratory (macacus monkeys, green monkeys, spider monkeys and small baboons). Since this holder, designed by one of us, has proved very satisfactory in this laboratory for the last four years, it is reproduced in figure 1.

Fig. 1.—Head holder for monkeys. *1* indicates an upright stand on the operating table; *2* and *3* are universal joint clamps; *4* represents the ground plate of the head holder; *7* shows a horizontal flat strip of brass, held down by two wing nuts on two blocks of ebonite. To the middle of this strip a brass tube is soldered horizontally, through which the animal can breathe. Around the intersection of the brass strip and the tube is placed dental cement, softened in hot water. Then the tube is introduced into the mouth of the narcotized monkey, and its jaws are closed. Thus, a cast of the teeth is taken and the cement walled up around the teeth. To the right of the two wing nuts mentioned two other wing nuts can be seen. With these the two brass strips $6_1$ and $6_2$ can be fixed. The curved ends of these strips are adjusted behind the ascending rami of the animal's mandibula and pushed forward as far as possible, whereupon the two wing nuts are screwed home. Thus, the head of the animal is held by the brass strip across the mouth, the cement cast of the teeth and the grip behind the mandibular rami. Finally, to complete the fixation of the head, a curved piece of brass, covered with rubber tubing (*8*), is tightened on the nose of the monkey with the universal clamp *3* fastened to the upright, *5*, in the ground plate, *4*, of the holder. If the cast of the animal's mouth is taken correctly, the head is fixed rigidly by this holder and can be adjusted in any desired position in space. The position of the head in relation to the holder is always the same, so that the head can be placed in any desired position by orienting the ground plate of the holder properly in space. The figure is one fifth of the actual size.

The position into which the head of the monkey was adjusted differed for the various routes of injection. In the case of a transverse or a sagittofrontal injection the hard palate of the animal was put in the horizontal plane; for a sagittooccipital injection the hard palate was placed at such an angle in relation to the horizontal plane that the desired thalamic nucleus could easily be reached.

*Examination of the Animal.*—Examination of each animal as to its sensibility was made while the animal was free to move at the end of a short chain fastened to a belt around its waist and to a ring in the center of a large table. In all but the first four experiments vision was excluded by sewing the eyelids of each eye together with two stitches. This procedure was found to be helpful in producing a quieter state in the animal. Even so, several of the animals were still found to react more or less wildly to any sensory stimulus applied. When such a case was encountered, the monkey was held by the nape of the neck in the air or in a squatting position on the observation table. This always induced a state of diminished activity, in which the reactions to sensory stimuli could profitably be studied.

Several sensory stimuli were used in each animal. For tactile stimulation the skin of various parts of the body was touched with a brush and with a blunt instrument and was pinched slightly with a forceps without teeth. For painful stimulation the skin was pricked with a needle and pinched with a toothed surgical forceps. Also, the reactions to pulling the hair with a forceps were studied. Finally, the reactions when the skin was touched with a warm or hot eye cautery were investigated and compared with those to contact with the unheated cautery.

Some animals before the strychninization showed asymmetrical reactions, although the stimuli to the two sides of the body were made as nearly equal as possible. Animals which presented such asymmetry were excluded from the actual experiment.

The course of one experiment, i. e., of an injection into the thalamus of one side, was therefore as follows:

The animal was anesthetized in the regular narcosis box with divinyl ether; its eyelids were sewed together, and when still under narcosis it was placed on the observation table. During the course of recovery from the anesthetic the reactions to the various sensory stimuli were studied as to intensity and symmetry. If these reactions were found to be symmetrical, the animal was anesthetized again with divinyl ether and placed on the operating table, and the head and head holder were properly oriented in space. Then the particular part of the central nervous system to be used as the point of entrance for the needle was exposed. The apparatus for micro-injection, with the syringe and needle filled, was now properly adjusted and firmly clamped to the operating table. In the case of a transverse injection a small area of the cortex at the point of entrance of the needle was cauterized. Then the syringe and needle were screwed forward by the rack and pinion until the point of the needle touched the cortex, when a reading on the millimeter scale alongside the rack and pinion was taken. Now the syringe and needle were screwed forward over the desired distance into the brain as measured on the millimeter scale. When the tip of the needle had reached the end of its intended course through the brain into the thalamus, the needle and syringe were withdrawn 0.5 mm. by turning back the screw of the rack and pinion. Then the intended amount of the solution of strychnine sulfate, from 0.5 to 2 cu. mm., was injected by driving the plunger of the syringe forward with the micrometer. Then the syringe with its needle was withdrawn by screwing back the syringe carrier on its rack and pinion. Finally, the wound in the skin was closed with a few stitches.

Nearly always one such experiment was performed on one side during the morning; a similar experiment on the other thalamus was made during the afternoon of the same day.

At the end of two such experiments the monkey was killed with ether and the brain fixed by injection of from 50 to 80 cc. of a 15 per cent concentration of solution of formaldehyde U.S.P. into each carotid artery. One hour later the brain was removed from the skull and cut into thin slices with a knife specially devised for this purpose.

These slices were photographed, and the location of the injection of strychnine in the thalamus was inscribed on large drawings of transverse cross-sections of the thalamus of the monkey at seven different levels (for details, see the section on functional localization).

## RESULTS

*General Symptomatology.*—Injection of strychnine into the thalamus of the monkey results, as in the cat, in marked symptoms of sensory excitation, especially hyperesthesia and hyperalgesia of the skin. These symptoms were always found to be present on both sides of the body; they were most pronounced on the side contralateral to the injection of strychnine and in the apical parts of the body (hands, feet and ears). Typical also were the long after-reactions to sensory stimulation.

After elimination of cutaneous sensibility by section of the cutaneous nerves, pressure on subcutaneous structures (muscles, tendons, bone and periosteum) elicited abnormally strong reactions only in the contralateral half of the body.

In several experiments characteristic symptoms of spontaneous, paresthetic sensory disturbances were evident. In a few experiments unmistakable symptoms of sensory "irradiation" were noticeable. It was observed, for instance, that in an animal in which symptoms of hypersensitivity existed in the arms and head, stimulation of the skin of the hand produced signs of abnormal sensation not only in that hand but also in the face and vice versa.

The symptoms of sensory excitation after intrathalamic strychninization gradually subside after from five to ten minutes and are no longer noticeable from forty to fifty minutes after the injection.

The symptomatology in these experiments on the monkey is essentially identical with that observed in the cat after local strychninization of the optic thalamus. Only minor quantitative differences were perhaps noticeable. We have received the impression that the paresthetic disturbances and the signs of irradiation were less pronounced in the monkey than in the cat.

*Functional Localization.*—Apart from the symptomatology, the outstanding feature of these experiments was the fact that the symptoms of sensory excitation in the various experiments were present in different parts of the body, depending on the locus of strychninization in the thalamus. The various thalamic nuclei are therefore in functional rela-

tion with different parts of the body. This means that there exists a functional localization in the thalamus of the monkey. We shall now discuss this localization.

As these experiments are fundamentally similar to those on the cat's thalamus, we refer the reader for general comments to the exposition in the previous paper [1] (pages 247 to 250).

As an anatomic guide we have made use of the Weigert-Pal maps of the thalamus of the macacus monkey, prepared by C. Vogt,[4] supplemented, if necessary, by the Nissl maps of Friedemann.[5] With a projection apparatus drawings, enlarged five times, were made of seven of the plates in Vogt's paper, representing transverse sections through the monkey's thalamus; in these drawings the locations of the various injections of strychnine were inscribed as accurately as possible. From these drawings reduced photographs (figs. 5 to 8 in the present paper) were made. The locations of the injections of strychnine which resulted in symptoms in the hindlegs are marked with squares; those which gave rise to sensory disturbances in the arms, with crosses, and those which produced symptoms in the head, with circles. This designation was also used in the previous experiments on the cat's thalamus; thus, comparison of the results of the two series of experiments is made easy.

In a few experiments microscopic preparations (Nissl) through the thalamus were made, which invariably showed that the macroscopic "diagnosis" of the localization of the injection was correct. As has been stated in the previous paper,[1] it is remarkable how easily, after a little experience, the exact location of the intrathalamic injections can be determined with sufficient accuracy without microscopic control.

We give here two illustrative protocols, one for an animal with a transverse and one for an animal with a sagittofrontal injection.

PROTOCOL 1.—*Macacus rhesus 54; April 18, 1935.*

10:30 a. m.: Divinyl ether anesthesia. Eyelids of both eyes sewed together. Animal on the observation table.

10:38 a. m.: Animal awake again and sitting up. No abnormal reactions to sensory stimuli and no differences in the reactions on the right and those on the left side of the body. Animal again anesthetized with divinyl ether and placed on the operating table. Head in the correct position in the space in the head holder, i. e., with the hard palate horizontal.

10:50 a. m.: Exposure of part of the right hemisphere. Injection of 1 cu. mm. of a 3 per cent solution of strychnine sulfate into the right hemisphere. Entrance of the needle into the cortex of the postcentral gyrus, just in front of the end of the interparietal sulcus. Cortex of this region killed by thermocoagulation. Downward inclination of the needle 30 degrees; needle also slightly directed from the occipital region and above toward the frontal region and below. Depth of injection 17 mm. Closure of wound in the skin with a few stitches.

4. Vogt, C.: J. f. Psychol. u. Neurol. **12**:285-324, 1909.
5. Friedemann, M.: J. f. Psychol. u. Neurol. **18**:309-390, 1911.

11:00 a. m.: Animal almost awake again and sitting up in the center of the observation table, at the end of its chain. Definite symptoms of hyperesthesia and hyperalgesia of the skin of both hindlegs, especially of the feet, most pronounced on the left. No abnormal sensitivity apparent in the arms and face.

11:10-11:15 a. m.: Marked symptoms of hypersensitivity of the skin of both feet, strongest in the left. Even when the animal is held by the nape of the neck, these symptoms are present. No signs of paresthetic disturbances.

11:40 a. m.: Symptoms are less evident than before, though still present. In the arms and face no abnormal sensitivity is noticeable. (In the afternoon the animal was used for another transverse injection, which we omit here.)

Necropsy: The injection was located, as was planned, in the lateral portion of nucleus 1bII of Vogt's map number 6 (picture 5, figure 2, showing occipital aspects of the slices of the brain).

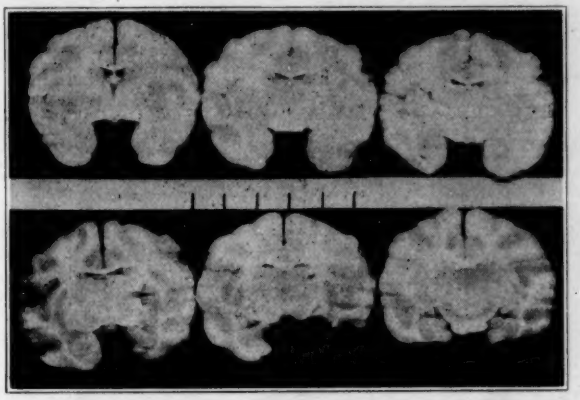

Fig. 2.—Cross-sections of the brain of monkey 54. In the fifth section the transverse intrathalamic injection into the lateral part of nucleus 1bII can be seen readily. Between the rows of sections a centimeter scale indicates the reduction.

PROTOCOL 2.—*Macacus rhesus 17, Feb. 4, 1935.*

Anesthesia with divinyl ether. Eyelids sewed together. On recovery of the animal from the anesthesia, examination revealed no abnormal reactions to the various sensory stimuli, especially no difference in the reactions elicited from the two sides of the body.

Animal anesthetized again with divinyl ether. Head in the correct position in space in the head holder.

2:25 p. m.: Injection into the left thalamus in the sagittal plane, 8 mm. from the medium plane of the skull; point of entrance of the needle 5 mm. above the left eyebrow. Needle directed at an angle of 15 degrees with the base of the skull. Depth of injection 35 mm.

2:30 p. m.: Animal sitting up, almost awake, on the observation table, but still a little drowsy. Strong hyperesthesia and hyperalgesia of the skin of both arms, especially of the hands. Symptoms strongest in the right hand. No obvious disturbances in the legs or face.

2:40 p. m.: Still marked hypersensitivity of the skin of both hands, strongest in the right hand. No disturbances in the legs and head.

Necropsy: The injection reached nucleus 1bIII (Vogt's maps 7 and 8) and nucleus 1bII (Vogt's map 6) (fig. 3).

Figure 4 shows a Nissl preparation of the thalamus of monkey 12 after a transverse injection into the right thalamus. The neat boundaries of the narrow needle track can readily be seen.

On the basis of eighty-seven experiments, such as are described here, the functional localization in the thalamus, depicted in the accompanying diagrams, was established (figs. 5 to 8).

Figure 5 *A* shows the most anterior portion of the thalamus, corresponding to the section in Vogt's plate 9. At this level strychninization

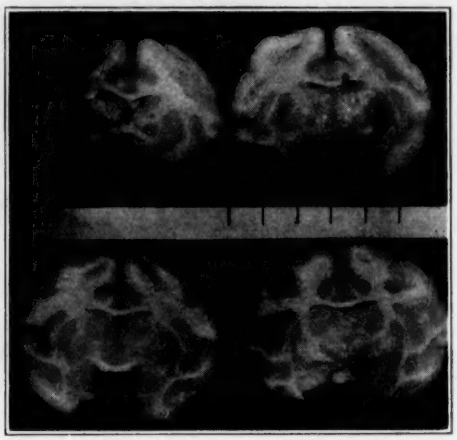

Fig. 3.—Cross-sections of the brain of monkey 17, with a sagittofrontal intrathalamic injection. In the first two slices the needle track lies in the internal capsule. In the third section strychninization is seen in nucleus 1bIII (see figure 6 *A*). In the fourth section the end of the needle track is barely seen in nucleus 1bII (see figure 6 *B*).

of nucleus 1bIII results in symptoms of hypersensitivity in the hindlegs (squares) and the arms (crosses). The hindlegs are represented more laterally than the arms.

Figure 5 *B* represents the portion of the thalamus corresponding to that shown in Vogt's plate 8. At this level nuclei 1bIII and 1bIV are fairly well developed. In the lateral portion of nucleus 1bIII the hindlegs are represented sensorially, and in nucleus 1bIV, the arms. Strychninization of the intermediate gray matter, between nucleus 1bIII and nucleus 1bIV, results in symptoms in the legs and arms simultaneously.

Figure 6 *A* shows the thalamus as pictured in Vogt's plate 7. Here nuclei 1bIII and 1bIV are large and fully developed. In the outer

stratum of nucleus 1bIII the hindlegs are represented exclusively, and in the medial portions, the hindlegs and arms; strychninization of nucleus 1bIV results in symptoms in the arms only. In nucleus Vtl the hindlegs and arms are represented.

Figure 6*B* corresponds to Vogt's plate 6. Here nuclei 1bI and 1bII are the sensory nuclei for the legs and arms; the legs are repre-

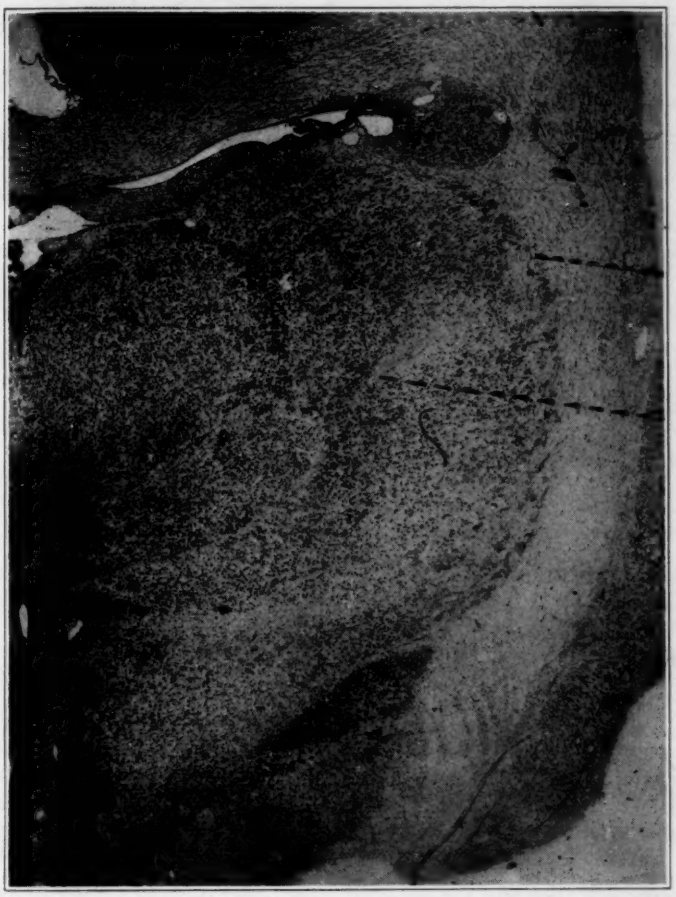

Fig. 4.—Nissl preparation of the thalamus of monkey 12 with a transverse injection into the ventral part of nucleus 1bII (see figure 6*B*). Ends of the needle track are indicated by dotted lines. Note the neat boundaries of the lesion by the needle. Magnification 12.

sented in the lateral and the arms in the medial portions. At this level nucleus Va[1] appears for the first time. In its ventrolateral portion at this level the legs and arms are found to be represeented. In a few experiments in which strychninization was found to have reached the

gray matter between nucleus Va[1] and nucleus 1bII symptoms of sensory excitation were observed in the face (circles).

Strychninization of the lateral nuclei c1bI, c1bII and Va at the level depicted in figure 7 *A*, corresponding to that in Vogt's plate 5, resulted in typical symptoms in the legs and the arms. Again, one finds the legs represented in the more dorsal and lateral parts of these nuclei and the arms in the ventral and medial portions.

In nucleus Vb (Vb[1] and Vb[2] of C. Vogt), which is fully developed at this level, a "pure" sensory representation of the head is found.

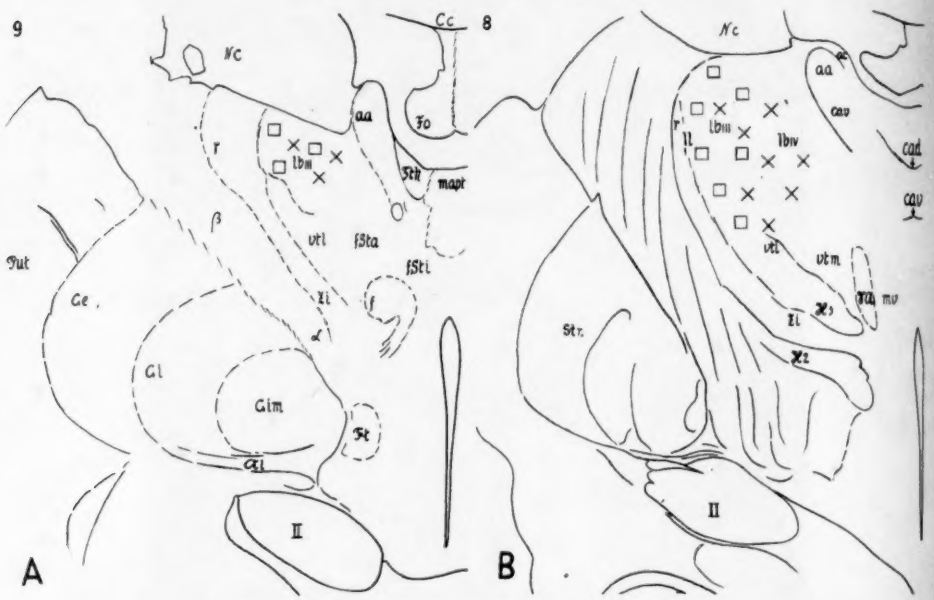


Fig. 5.—(*A*) The most frontal cross-section of the thalamus (C. Vogt's plate 9), showing the sensory functional localization for the hindlegs (squares) and for the arms (crosses) in nucleus 1bIII. (*B*) A more occipital cross-section through the thalamus (C. Vogt's plate 8). In nuclei 1bIII and 1bIV the hindlegs and arms are represented sensorially, the hindlegs more laterally.

Figure 7 *B* pictures the level of the thalamus corresponding to that in plate 4 of C. Vogt. In nucleus c1bI and nucleus c1bII, and also in the dorsal portion of nucleus Va, the legs and arms are represented, and in the ventral portion of nucleus Va the head is represented.

In figure 8, corresponding to Vogt's plate 3, in which most of the thalamus is shown to consist of the pulvinar, only the posterior pole of nucleus b (C. Vogt.) is present. Its strychninization results in symptoms of sensory excitation of the head. Strychninization of the various parts of the pulvinar does not result in apparent sensory disturbances.

In several experiments strychnine was injected into the medial nuclei (mag, mapt and m$\alpha$ of figure 6 *A;* maga and m$\alpha$ of figure 6 *B,* and magp, mapl, m$\alpha$ and mb of figure 7 *A*), which did not result in appreciable symptoms of sensory excitation. It is assumed, therefore, that in the monkey the medial nuclei of the optic thalamus are not endowed with sensory functions. This point is of interest because strychninization of the medial nuclei in the cat gives rise to definite symptoms of sensory excitation.

It should be noted that here, in the thalamus of the monkey, as in that of the cat, the various regions for the different parts of the body

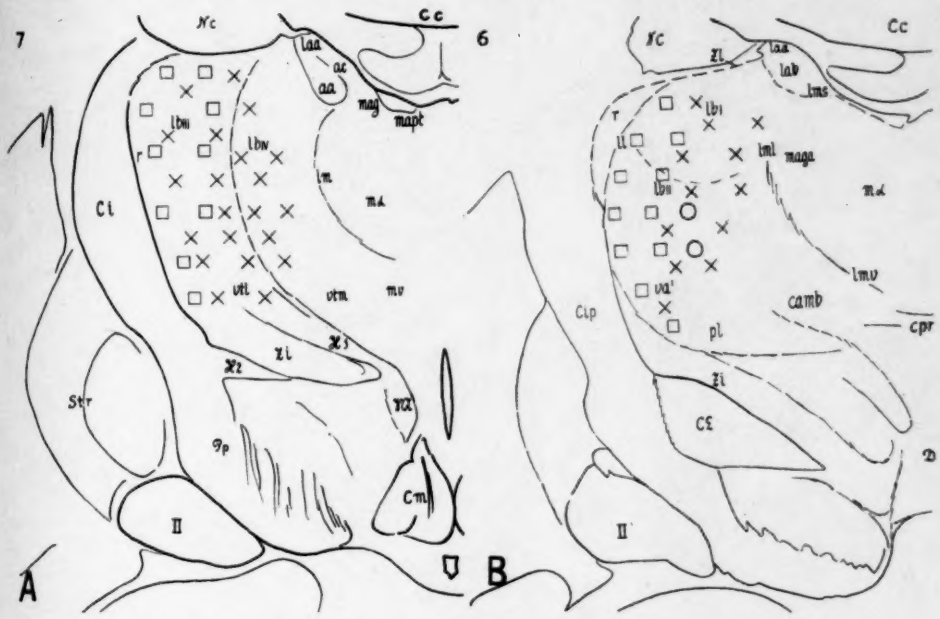


Fig. 6.—The cross-section in *A* corresponds to that in Vogt's plate 7. In nuclei 1bIII, 1bIV and Vtl the sensory representation of the hindlegs and arms is observed. The hindlegs are again more laterally represented. *B* corresponds to C. Vogt's plate 6. The hindlegs and arms are represented in nuclei 1bI and 1bII and the lateral portion of nucleus $Va^1$. In the gray matter between the medial parts of nucleus 1bII and nucleus $Va^1$ the first representation of the head appears. No sensory representation appears in the medial thalamic nuclei maga and m

overlap to a considerable extent. This is true especially of the regions for the hindlegs and arms, although also of these regions and the area for the head (figs. 6 *B* and 7 *B*). On comparison of the functional localization in the thalamus of the cat with that of the monkey it seems to us that regional overlapping is more pronounced in the cat's thalamus. In accordance with this is the observation that sensory irradiation was

observed less frequently in the experiments of this series than in those on the cat. In nucleus Vb of C. Vogt, or Flechsig's nucleus semilunaris, the head is represented sensorially exclusively, without any overlapping from the adjacent territories for the arms.

Perhaps the easiest way to visualize the spatial factor in this localization is to see the various sensory nuclei of the monkey's thalamus as a mass of gray matter forming a broad cone, with its apex in the medioventro-occipital portion of the thalamus, its axis running in a laterodorsofrontal direction and its base the external surface of the thalamus (zona reticularis), bordering the posterior segment of the

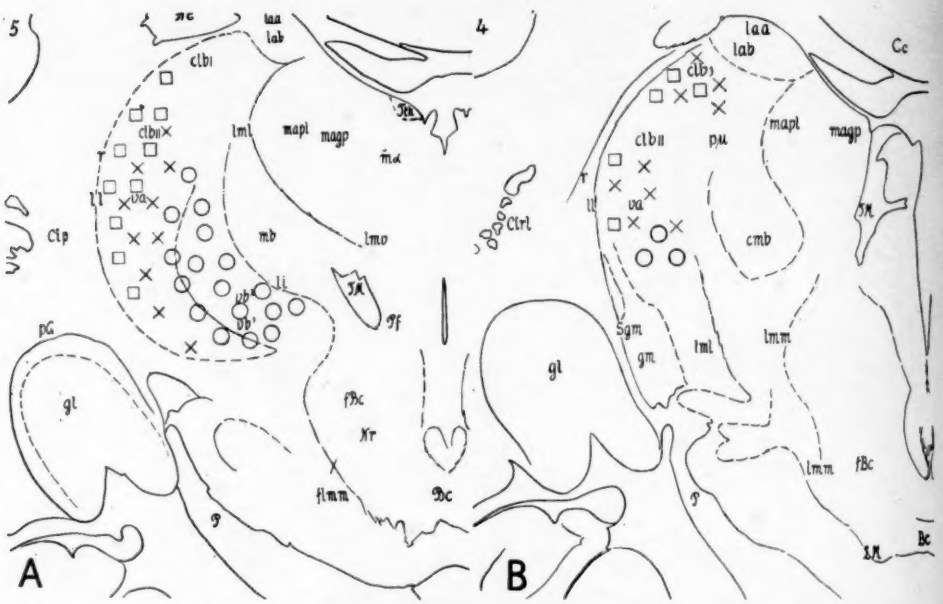


Fig. 7.—*A* corresponds to Vogt's plate 5. In nuclei clbII and Va the hindlegs and the arms are represented, the legs more laterally. The entire formation of nuclei $Vb^1$ and $Vb^2$ is taken up by the sensory representation of the head. No sensory symptoms were observed on injection of strychnine into the medial nuclei mapl, magp and ma. *B* corresponds to C. Vogt's plate 4. In nuclei clbI and clbII and the dorsal parts of nucleus Va the sensory representation of the hindlegs and arms is observed. In the ventromedial parts of nucleus Va the head is represented.

internal capsule. The apical third of this cone is taken up by nucleus Vb (C. Vogt), in which the head is represented, and the outer two thirds, by the lateral and ventral thalamic nuclei ($lb,^{I}$ $lb,^{II}$ $lb,^{III}$ $lb,^{IV}$ Va and Vtl). In the basal third of this cone the legs are represented sensorially, and in the middle third, the arms; both sections overlap extensively.

In some of the experiments strychnine was inadvertently injected into the cerebral ventricle as the needle passed through it. It is of interest to note that such an injection results in enormous hyperesthesia and hyperalgesia of the entire body, with marked paresthetic disturbances and fits of rage, panting, generalized hyperreflexia and the appearance of symptoms of a general discharge of autonomic effectors (salivation, vomiting, diarrhea, micturition, dilatation of the pupils, erection of the hairs, etc.).

In conclusion, we wish to point out that the functional localization established by these experiments agrees satisfactorily with the observa-

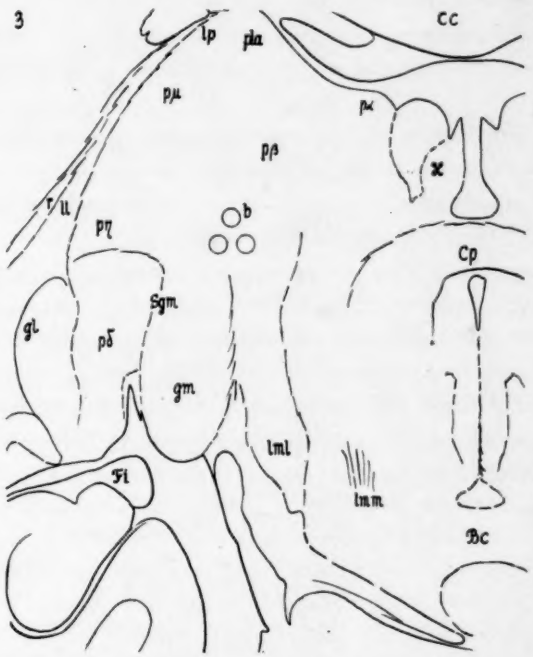


Fig. 8.—This figure corresponds to plate 3 of C. Vogt's paper and is a cross-section through the most occipital portion of the monkey's thalamus, which is almost exclusively taken up with the various subdivisions of the pulvinar. Strychninization of these parts does not result in sensory disturbances. In the center is nucleus b of C. Vogt, strychninization of which results in definite symptoms in the head.

tions of the recent investigations on the anatomic connections between the cerebral cortex and the thalamus. We refer to the well known papers of Le Gross Clark, Poljack, Sager, Mettler, Walker and others. However, we shall not enter into a discussion of this interesting matter; we prefer, rather, to present the physiologic observations and results as such.

SUMMARY

1. The sensory functions of the thalamus of the monkey (Macacus rhesus) were investigated with the method of local strychninization (injection of a minute quantity of strychnine into the thalamus). Eighty-seven successful experiments were performed.

2. Local strychninization of certain thalamic nuclei of the monkey (see paragraph 7) results in the following symptoms of sensory excitation: (*a*) hyperesthesia and hyperalgesia of the skin; (*b*) hypersensitivity to pressure of the deeper structures (muscles, tendons and periosteum) after elimination of cutaneous sensibility, and (*c*) paroxysms of paresthetic disturbances.

3. The disturbances in cutaneous sensitivity are always present bilaterally and are strongest on the side of the body contralateral to the injection.

4. The disturbances in deep sensitivity are present only on the side contralateral to the intrathalamic injection.

5. The disturbances are invariably most pronounced in the apical parts of the body (ears, hands and feet).

6. In the monkey local strychninization of the medial thalamic nuclei does not result in appreciable sensory symptoms. It is assumed that in the monkey these nuclei do not subserve sensory functions.

7. A functional localization exists in the lateral, ventrolateral and ventral nuclei of the monkey's thalamus, which is described and depicted.

8. Irrespective of the location of the injection of strychnine in the nuclei mentioned (paragraph 7), the symptomatology is apparently identical.

# ELECTRICAL STIMULATION OF THE CORTEX CEREBRI OF CATS

## RESPONSES ELICITABLE IN CHRONIC EXPERIMENTS THROUGH IMPLANTED ELECTRODES

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Although much has been done to advance knowledge of the effect of electrical stimulation of the cortex cerebri in various species of animals since the primary work in this field, interpretation of the results has been difficult because of the multiple factors for variation which appear in every experiment. One of the most potent influences for variation of responses to cortical stimulation is the state of anesthesia. During the exploration of cortices of normal cats we frequently observed that a state of lightness of anesthesia was accompanied by a lowered threshold to stimulation and, conversely, that when the cat began to make spontaneous movements because of the lightness of anesthesia and the ether supply was increased, it was immediately necessary to increase the strength of stimulus to produce the usual response from a point. The depth of narcosis could be made so great that the cortex failed to respond to stimuli, however strong, except by a twitch of neck and shoulder muscles, which was considered to be due to a generalized spread of the stimulus, as the same effect was observed by direct stimulation of the dura mater or the subcutaneous tissues. The areas, therefore, which were mapped out as being those responsible for certain movements in the normal cat [1] were obtained from cortical stimulation when the cat was neither too lightly nor too deeply anesthetized. The conduction of such a series of observations involved considerably the factor of personal judgment, and it was with the idea of eliminating at least the variable influence of anesthesia that the present investigation was undertaken.

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From the Department of Anatomy, the Vanderbilt University School of Medicine.

1. Ward, James W., and Clark, Sam L.: Specific Responses Elicitable from Subdivisions of the Motor Cortex of the Cerebrum of the Cat, J. Comp. Neurol. **63**:49, 1935.

## METHOD AND MATERIAL

Twenty cats were successfully experimented on, and in each a small opening was made in the skull with a trephine so that the center of the aperture was approximately over the spot on the brain which was to be stimulated. When this spot was in the motor area, it was usually necessary to open the frontal sinus first and make the opening with the trephine in its posterior wall. Into this opening, after the dura mater was laid back, was screwed a threaded stainless steel plug, in the center of which was a cork or rubber stopper pierced by a silver wire. The silver wire extended for about 1 mm. beyond the inner face of the stopper and so rested on, or pierced slightly, the cortex cerebri. The inner edge of the plug was flush with the inner surface of the skull. In some animals, after the failure of the first electrode, a second was planted at a later date, and in two animals two plugs were planted at the first operation.

In the first ten animals a method similar to that used by Loucks [2] and by Chaffee and Light [3] was employed of planting beneath the skin of the scalp a flat coil of many turns of fine wire, one terminal of which was soldered to the silver wire reaching the brain and the other to a silver disk placed subcutaneously as an indifferent electrode. The leads and the coil were properly insulated and, except for infection introduced at times through the frontal sinus, were involved in no serious reaction.

When it was desired to stimulate one of these animals, a primary coil obtaining its energy by way of a variable step-down transformer from the 110 volt, 60 cycle lighting circuit was brought near the implanted secondary coil. The small transformer was capable of delivering currents from its secondary terminals of 4, 7, 10, 13 and 15 volts and was easily controlled by a lever switch sliding over contacts.

The primary coil used for stimulating was made of a number of turns of heavy copper wire around a central core of iron wires. The secondary coils planted in the cats varied in size and ranged from 1,200 to 2,800 turns.

In order to stimulate the spot on which an electrode was planted, the transformer was set at its lowest voltage, and the primary stimulating coil was brought toward the cat's head for a definite length of time. If this did not produce an effect, the voltage at the transformer was increased and the process repeated until a response was obtained. Such currents as were used could be easily borne on the tongue when the coils were tested previous to planting.

In the second group of ten animals, instead of a secondary coil beneath the skin, only a steel plug containing the silver electrode was planted. The plug was extended into a tube which pierced the skin and was sealed to it with a layer of flexible collodion. To stimulate these animals one of three methods was employed. First, a small secondary coil incased in a metal box, its terminals fastened to a small plug which could be inserted into the tube projecting from the cat's skull, was used just when a stimulus was to be applied. The primary stimulating coil was brought close to this secondary coil on the outside of the cat's head. The

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2. Loucks, R. B.: Preliminary Report of a Technique for Stimulation or Destruction of Tissues Beneath the Integument and the Establishing of Conditioned Reactions with Faradization of the Cerebral Cortex, J. Comp. Psychol. **16**:439, 1933.

3. Chaffee, E. Leon, and Light, Richard U.: A Method for the Remote Control of Electrical Stimulation of the Nervous System, Yale J. Biol. & Med. **7**:83, 1934.

silver wire in contact with the brain acted as the stigmatic electrode, and the stainless steel cuff passing through the tissues, as the indifferent electrode (the face of the plug in contact with the brain was insulated, as was that of the rubber stopper and all but the tip of the silver wire, with a coating of pyroxylin in most instances, but the omission of this coating seemed to make no difference in the results). Since movements of the cat from stimulation caused variation in the applied stimulus with this arrangement, as it did in the first group, the coil was fastened to an extension of flexible wire which was plugged into the tube projecting from the cat's head, one wire making contact with the silver wire piercing the rubber plug and the other with the tube itself. This second method of stimulation was the most useful, since the cat had much freedom and did not mind, or even seem to notice, the wire connected with the terminal on its head. Measurements of the currents used in stimulating were made from the tips of the wires used in the extension cord where they made contact with the plug in the cat's skull. The voltages delivered at the end of the extension cord when the variable transformer was set for 4, 7, 10, 13 and 15 volts were, respectively, 0.1, 0.3, 0.5, 0.6 and 0.75 volts. The strength of current for the position of 15 volts on the transformer (0.75 volts at the tip) was approximately 0.7 milliampere and was less for the other positions. This does not represent the actual current reaching the cells of the cortex, for the resistance of different animals and that of the terminal contacts varied. For more accurate stimulation the leads to the cat's head were attached by an extension to an oscillator capable of delivering currents of measured strength, varying in frequency from 15 to 10,000 or more cycles per second. This method of stimulation was of value in studying the thresholds of various responses.

The animals recovered rapidly from the operation and were ready for experimental testing immediately, though the anesthetic (pentobarbital sodium, 30 mg. per kilogram of body weight) affected the response obtained for several hours after implantation. The stainless steel plug was not visibly affected by the tissue juices, and as it fitted closely into the opening in the skull, loss of cerebrospinal fluid was prevented. Furthermore, it appeared to act as a barrier against the penetration of purulent material that developed in the frontal sinuses of some of the cats after several days. The preparation was effective for two or three weeks, and then the plug screwed into the bone tended to loosen as the bone altered about it, though cat 47 remained in good condition for more than seven weeks.

The effect of stimulation was determined immediately after the operation, while the effect of the anesthetic was maximal, as well as during the next day, before recovery was complete. Such observations were compared with the effect of stimulation when the animal had recovered entirely and with that during subsequent experimental etherizations in some animals. In order to stimulate the cats while they were being anesthetized with ether, a tight box with a glass top was constructed, into which was blown a jet of air containing ether vapor. With a manometer for determining the air pressure and a buret for measuring the ether, it was possible to put into the box a definite quantity of ether in a definite time; from 6 to 7 cc. of ether evaporating into the stream of air each minute caused the average cat to become anesthetized in about thirty minutes. Through two openings in the box the forearms of the experimenter were thrust to manipulate the stimulating coil. These openings were made in a sponge rubber sheet which fitted closely about the arms and prevented excessive leaking of air.

## RESULTS

In fifteen of the cats in this series the stimulating electrode was placed on some part of the motor area, and in most of these it was located on the anterior sigmoid gyrus, in the neighborhood of or on one of the spots which we have observed to respond to stimuli in the anesthetized animal with rhythmic "batting" or "digging" movements of the contralateral forelimb. As the electrode was fixed in position, it was possible to stimulate repeatedly and at long intervals the same cortical point, a procedure which is practically impossible with an electrode held in the hand, even in an acute experiment.

Perhaps the most significant observation made in these experiments was that of the constancy of response to stimulation of a cortical point. Naturally, it was not possible to place the electrode in exactly corresponding points in different cats; so the responses were not identical in any two animals, but each had its characteristic response to stimulus, which was shown at autopsy to have been determined by the position of the electrode in relation to the small subdivisions of the motor cortex that have been identified with specific movements. Each cat, therefore, responded from day to day with fundamentally the same pattern of movement. This movement could be modified in the individual cat in a number of ways—for example, by varying the strength or duration of the stimulus, by administering an anesthetic, by giving stimuli at sufficiently close intervals for facilitation to become effective or for fatigue to enter in, by altering the position of the cat or by operation on other parts of the nervous system.

The character of the movements produced in the different cats requires special consideration. First, it was noted that movements other than what may be termed the primary response for the specific cortical point were much more easily elicited in the unanesthetized than in the anesthetized animal. In an unanesthetized cat, when a stimulus is applied to the electrode in contact with a point on the motor area that responds primarily with a digging movement, for example, it is possible to time and grade the stimulus so that this movement is all that occurs. Such movement, for the sake of convenience, may be called primary. Prolongation of the stimulus, however, or increasing its strength or varying it in both these ways usually results first in the movement already obtained with less stimulation and then in spread or "march" of contractions to other regions of the animal's musculature. Rhythmic movements of the hindlegs, for example, may follow, or even accompany simultaneously the use of the forelegs, or some type of turning the head or activity of the facial muscles may break through. The muscles involved in movement depend on the position of the electrode.

If the stimulus is prolonged or strengthened sufficiently, there may be an after-effect which persists a while after cessation of stimulation.

In these experiments the primary movements resulting from stimulation of spots in or adjacent to the motor area were invariably contralateral. If the stimulus was strengthened or lengthened, however, so that an after-effect came in, movements of the homolateral muscles might appear. Or if the primary movements were of such character as to alter the posture or balance of the animal, other movements entered as a part of the reflex adjustment to its new position.

It has been mentioned that the muscles involved in the primary motion elicited by stimulation depended on the position of the electrode on the brain. Brief descriptions follow of the results obtained in several cats with electrodes on different parts of the brain. In the other cats in the series the results were practically duplicates of some of these described. Since much of the motor area in the cat surrounds the cruciate sulcus, it is convenient to indicate the position of the point stimulated by reference to that sulcus. The cruciate sulcus extends from the median sagittal fissure, and while it varies slightly in length and position in different animals, in a typical case it ended 9 mm. lateral to the fissure. Its end was then 5 mm. from the coronal sulcus laterally and 6 mm. anteriorly, and 9 mm. from the junction of the lateral and ansate sulci posteriorly (fig. 1).

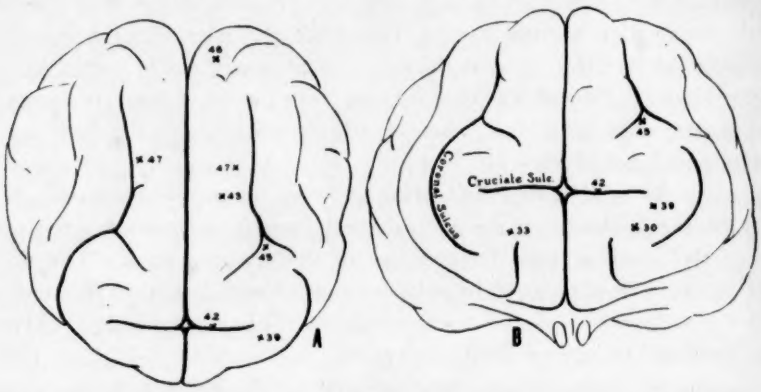
In cat 30 mild stimulation after recovery from the anesthetic gave pure rhythmic batting of the contralateral foreleg, with no other response unless the stimulus was strengthened or unduly prolonged. The point was observed at autopsy to have been placed 7 mm. lateral to the midline and 4 mm. anterior to the cruciate sulcus. This corresponds closely to the "batting" point previously described.

In cat 33, with the electrode planted on the right side, there was rhythmic lifting of the left foreleg, associated with turning of the head. When the stimulus was prolonged, the cat rotated its head toward the left (with the jaw to the right), lay on its left side and turned over. The electrode was observed to have been located just lateral to the upper end of the presylvian sulcus, 5.5 mm. from the midline and 4.5 mm. anterior to the cruciate sulcus.

In cat 42 the primary motion was rhythmic flexion of the hindlimb, accompanied by rhythmic flexion of the forelimb only when the stimulus was prolonged. The after-effects of a strong stimulus in this cat involved such marked lifting of the right hindleg that the cat tended to fall over on the other side. The electrode was placed about half-way along the cruciate sulcus (4 mm. from the midline) and in contact with the pia mater as it dipped into the sulcus, thus being in a position where it could affect the cortex of both the anterior and the posterior margin of the cruciate sulcus. At this point the hindlimb area lies on both sides of the cruciate sulcus.

In cat 45 the electrode was placed 9.5 mm. behind the cruciate sulcus, just in front of the bifurcation of the lateral into the ansate sulcus. If a mild stimulus was applied, after a period of summation (the time elapsing between onset of the stimulus in the motor cortex and the first appearance of a discharge from the final motor neurons [Cooper and Denny-Brown [4]]) which lasted sometimes for several seconds, depending on the strength of stimulus and the history of stimulation just preceding, the contralateral hindlimb began rhythmic flexion. If the stimulus was continued, the foreleg might also begin rhythmic lifting. The length of the period of summation in this animal demonstrated a distinct difference between the response of a point not in the motor area and that of one directly in it.

In cat 43 the electrode was planted 22 mm. back of the cruciate sulcus, in the left lateral gyrus (about half-way between the cruciate




Semidiagrammatic drawing of the brain of a cat from two slightly different points of view: *A*, from the dorsal surface, and, *B*, from the anterior end of the cerebrum. The crosses indicate location of the electrodes in cats the numbers of which are placed alongside. The points are indicated for only those cats described in the text. The drawings were made under a camera lucida and the spots placed by superimposing the image of each brain on the drawing under the camera lucida.

sulcus and the occipital pole). When stimulation was made with a weak current, there was first withdrawal of the head, straight back with no deviation to one side or the other; the palpebral aperture narrowed and the eyes dilated slightly. When the stimulus was strengthened (the cat was seated, with the hindlegs bearing the weight), the contralateral foreleg lifted, and with cessation of the stimulus the foreleg jerked in a clonic after-effect. Still stronger stimulus caused both contralateral legs to contract rhythmically. Movements in this cat followed stimula-

4. Cooper, S., and Denny-Brown, D. E.: Responses to Stimulation of the Motor Area of the Cerebral Cortex, Proc. Roy. Soc., London, s.B **102**:222, 1927.

tion after a period of summation of four or five seconds. When the animal was gradually anesthetized, stimuli applied as the state of narcosis deepened had to be strengthened and lengthened to produce the usual response. For example, shortly after the beginning of etherization a stimulus lasting four seconds produced a good response of the foreleg (the cat being seated), with the after-effect lasting eight seconds. After ten minutes in the ether box a stimulus of the same strength as before, lasting seven seconds, produced only a slight movement of the foreleg, which ceased promptly with the stimulus.

When an electrode was planted much farther back of the motor area, as in cat 46, in which it was placed on the lateral gyrus just in front of the occipital pole, there was no obvious response to brief stimuli, either weak or strong, but after prolonged weak stimulation there was a tendency for the cat to turn its head to the opposite side, as if looking around. A mild stimulus of fifty-six seconds' duration resulted in an epileptiform seizure which lasted in its various phases three minutes after cessation of the stimulus (Ferrier [5] observed a cat to look around "in an astonished manner" from stimulation of a point near this location).

In cat 49 the electrode was planted in the anterior end of the middle suprasylvian gyrus where stimulation in the anesthetized animal produces movements of the contralateral ear. This cat suffered unidentified lameness in first the homolateral and then the contralateral foreleg, lasting for a week after the operation. The animal completely recovered, and the placing reactions in all extremities were normal. After recovery from the illness the responses to stimuli were similar to those obtained before. Thirty days after implantation a brief stimulus (two seconds) produced apparently simultaneously slight narrowing of the palpebral aperture, dilatation of the pupils and drawing back of the contralateral ear. If the stimulus was prolonged slightly, twitching of the ear continued after cessation of the stimulus. A still more prolonged stimulus provoked an epileptic attack in which the muscles of the ear, whiskers, jaw and tongue on the opposite side made clonic movements, followed by clonic lifting of the contralateral hindlimb, then by that of the contralateral forelimb and so on. Such an attack required two minutes or more for completion, and the cat showed signs of weakness for a while afterward, during which time the placing reactions were disturbed in the contralateral limbs.

The position of the cat while being stimulated at times caused variation in the response. For example, with a certain strength of stimulus, cat 39 when seated showed only contraction of the forelegs, but when the cat was suspended by the neck and tail or supported beneath the

5. Ferrier, David: Experimental Researches in Cerebral Physiology and Pathology, West Riding Lun. Asyl. Rep. **3**:30, 1873.

body, the same strength of stimulus provoked rhythmic movements of the forelegs and hindlegs simultaneously (the point in this cat was located just 2.5 mm. anterior to the lateral end of the cruciate sulcus).

The simplest response to stimulus was one in which the primary movement appeared, enduring only as long as the stimulus lasted. Usually, when a stimulus was strong enough or long enough to bring in movements other than the primary, the response did not stop with cessation of the stimulus but continued for a variable period. If the stimulus was just a little above threshold, this after-effect persisted a short while and gradually ceased. If the stimulus, however, was much greater than was necessary for the primary movement, the after-effect, instead of lessening, might show an increase until all the somatic musculature, and even some visceral structures, were involved and the animal experienced a prolonged epileptiform seizure. During such a seizure and for some time afterward, the response to stimulation was altered in that a much greater stimulus was necessary to provoke an equivalent response than was the case before. Furthermore, certain placing reactions in the affected extremities were disturbed. The study of such epileptic attacks will form the subject of a subsequent paper, but a description of one of them is of interest in the present report. The length of stimulus necessary to provoke epilepsy varied with the position of the electrode, with the immediately preceding history of the animal and with the strength of current.

A description follows of one of these attacks in cat 39, which gave rhythmic movements of the foreleg with mild stimulation of the implanted electrode.

After cessation of a stimulus which had lasted about fifteen seconds, the contralateral foreleg, which had been undergoing marked rhythmic movement during the stimulus, drew up against the animal's chest with twitching (the cat was being held by the neck and tail but was then placed on a table). Then the other foreleg became involved, followed immediately by contraction of the muscles of the back and both hindlegs. A generalized clonic convulsion developed, involving all the musculature, especially of the extremites. The claws were all extended. The contralateral eye remained closed for a while after a few spasmodic closures; chewing movements occurred; the back arched, and running movements began; some salivation occurred, and the pupils were widely dilated.

As the clonic state ceased, tonic extension of the hindlegs ensued, with marked flexion of both forelegs. The cat was now lying on its right side. It was placed on its feet, but with its extended hindlegs, arched back and lowered head, it almost turned a forward somersault and fell over. After a short time it began crying wildly, staring but not seeming to see. Soon the cat began to respond when its back was stroked; its cry changed to a plaintive tone; it looked about inquiringly, and within a short interval seemed to become normal, except for apparent weakness. The whole attack lasted about three and a half minutes, though the cat seemed less active for some time afterward.

This picture is typical in general of the epileptiform attacks produced in the various cats. In several fluffing of the hair on the tail occurred toward the end of the fit, and in one emptying of the bladder occurred, apparently accompanying clonic contractions of the abdominal muscles. Once, in cat 47, about one minute after the beginning of an epileptic attack, urination occurred when the abdominal muscles were not tense. In several instances salivation was observed, and pupillary dilatation was a common accompaniment of such attacks.

The results of these experiments confirm the observation of local subdivisions in the cat's motor cortex that are specific in their response. The absence of anesthesia apparently enlarged the excitable area of cortex, since movements of the forelimb and hindlimb were obtainable (when stimulation was sufficient) over wider areas than with anesthesia and specific movements, such as batting or digging, could be elicited from much wider areas than in the anesthetized animal. No doubt this was due to the greater capacity of the cortex for facilitation in the absence of anesthesia. A point, for example, back of the postcruciate sulcus in cat 45 produced on stimulation rhythmic flexions of the hindleg with much greater ease than when such a point is stimulated in the anesthetized animal. In fact, the anesthesia must be very light for the region about this point to be facilitated at all for activity of the hindleg.

This apparent enlargement of the excitable area of the cortex results in a greater overlapping of areas giving rise to specific movements than appears in the animal under deep anesthesia. During our original explorations of the cat's motor cortex, we found that the anesthesia could be kept at such a level that the spots in the motor area which responded with specific movements were well isolated and that the line of junction between the areas of the forelimb and those of the hindlimb was quite sharp, the responses being obtained from different extremities when two spots less than 1 mm. apart were stimulated. In subsequent experiments (unpublished) performed as a preliminary to the present work, the cortices of four cats were explored with the anesthesia kept just deep enough to prevent marked spontaneous movements. With this minimal narcosis there was found to be a greater tendency for the two limbs on one side to respond to stimulation of single spots. A brief description of typical results obtained in these cats will illustrate this.

With the cat under ether anesthesia, the cortex was exposed and the animal mounted on the rack used in previous experiments. The "batting point" was located and a fixed electrode placed on it as a mark. Then, with a wandering electrode, points between this and the cruciate sulcus and points beyond the cruciate sulcus were stimulataed. Near the cruciate sulcus both the forelimb and the hindlimb appeared in the responses, but farther away only single limbs were involved. By the excursion method of stimulation (stimulation of successive

points from 0.5 to 1 mm. apart in a line, with an interval of about one second between stimuli), the variation in the effect of stimulation of different points plus the influence of facilitation could be well demonstrated. Such an excursion from a point near the anterior end of the coronal gyrus directly in line with the electrode fixed on the batting point and extending through this and beyond the cruciate sulcus to the region of the postcruciate sulcus gave in cat 27 the following results: At the anterior end of the line, near the coronal gyrus, no effect was produced, but as the batting point was approached, batting in slow rhythm commenced, with marked forward extension of the limb. As the batting point was reached, the rhythm speeded up to its usual rate (from six to seven strokes in ten seconds), still with marked reaching forward of the arm. Back of the batting point the reaching and supination became less until the leg was merely lifted in rhythm. Back toward the cruciate sulcus the hindleg began to lift simultaneously with the movement of the foreleg, and as the cruciate sulcus was crossed, the movements of the foreleg dropped out, while the hindleg began to acquire a backward component of its movement until it was kicking straight backward. A short way behind the cruciate sulcus, movements of the hindleg also ceased.

Such an excursion was repeated in this cat and in other cats, with essentially similar results. Varying the direction of the line of excursion varied the responses which were obtained, dependent on the region crossed. If the excursion passed lateral to the batting point, for example, rhythm was soon lost, while sustained contractions of the foreleg were obtained and no response of the hindleg appeared.

## COMMENT

Leyton and Sherrington,[6] studying the motor cortex of higher primates, concluded (page 218):

> Although the broad localization of the responses of the various main motor parts of the opposite half of the body follows a well fixed topographical scheme in this cortex, the minute localization, as examined by faradization, is subject to temporal instability. This instability is largely the expression of mutual influences exerted transiently by the physiological states for the time being of different points of the motor cortex, and of the sub-cortical centres they connect with one upon another. These influences make themselves felt as "deviation of response," "reversal of response," and "facilitation" phenomena all seemingly akin.

It is obvious that this statement supports the belief in the specificity of responses from cortical points, variations being merely temporary alterations associated with the physiologic state, although the experiments of Franz[7] and others would imply that within the larger divisions of the motor area associated with the limbs, face, etc., the smaller subdivisions have no permanent connection with specific movements. Lashley,[8] for instance, after repeated examinations of part of the motor

6. Leyton, A. S. F., and Sherrington, C. S.: Observations of the Excitable Cortex of the Chimpanzee, Orang-Utang, and Gorilla, Quart. J. Exper. Physiol. **11**:135, 1917.

7. Franz, Shepherd I.: Variations in the Distribution of the Motor Centers, Psychological Monograph, no. 81, Princeton, N. J., Psychological Review Company, 1915, pt. 2.

8. Lashley, K. S.: Temporal Variation in the Function of the Gyrus Precentralis in Primates, Am. J. Physiol. **65**:585, 1923.

area in the same monkey, with long intervals between the examinations, came to the conclusion that in any one test the movements obtained from specific points were quite constant, while "in the tests on different days there was almost no constancy of reaction from day to day."

The points which we stimulated in unanesthetized animals responded consistently with the same movements from time to time over a period of weeks when there was a sufficient interval between stimuli. As already pointed out, the magnitude of the response could be varied by changing the stimulus, and the quantity of the musculature involved could be varied in like manner, this being evidence of facilitation of neighboring or connected centers.

During a relatively short period following a stimulus (varying in length with the character of the stimulus), there is a changed response from a cortical point, and this can well be described as "temporal instability." There is, however, an apparently permanent capacity in cortical motor points to respond to successive stimuli with the same type of response as a whole when the space of time between stimuli is sufficient for recovery.

In the experiments of Leyton and Sherrington [6] only two muscles of an extremity were left innervated, and cortical points which would produce contraction or inhibition of these muscles were found and stimulated with a wandering electrode. Lashley [8] also used a wandering electrode and depended on a graph of the area for finding the same spot in successive experiments. From our experience with the wandering electrode, it is easy to believe that in animals with intact innervation of the extremities the electrode could not always be placed on the same cortical point in successive stimuli. By varying the position of an electrode in the cat a fraction of 1 mm., it is possible to alter the character of the movement obtainable on stimulation. A change from batting to digging can result when the electrode is moved only 1 mm. in the proper direction.

Since Leyton and Sherrington did not have the whole limb to observe, some of the changes in tension in the two isolated muscles which they interpreted as deviation or reversal from stimuli arising from the same cortical point might have been due to slight changes in position of the stimulating electrode. Granted that a single point will repeatedly give the same response when stimulated, the question still remains whether specific movements are associated with specific groups of cortical neurons, since the areas from which more or less specific movements can be obtained are relatively wide in the unanesthetized animal. The results obtained from anesthetized animals have a distinct bearing on the question. In the original experiments, as ether was pressed to the point at which no spontaneous movements of the animal occurred,

there were, as we reported, small areas from which specific movements were obtained lying adjacent to areas from which quite different movements were produced on electrical stimulation. If the ether was pressed even further, these areas could be depressed in excitability, requiring stronger stimuli to produce their responses, and could finally be made unresponsive to electrical stimuli when the etherization was sufficient. Spots which could be facilitated for definite motions in lightly anesthetized animals gave no response as the anesthesia was deepened. Cessation of ether inhalation then allowed gradual return of excitability to the cortex. This is an experience common to investigations of the cortex of anesthetized animals and is no doubt correlated with the findings of Derbyshire, Rempel, Forbes and Lambert [9] on altered action potentials in the cat's cerebral cortex following anesthesia.

The results of anesthesia on the animals with implanted electrodes were similar. When an animal was put in the ether box and stimulated at regular intervals, there was observed, as it was gradually narcotized, gradual diminution in the quantity of the motor response to the same stimulus.

Similarly, with pentobarbital sodium used for the operations, it was common to observe much less response immediately after implanting the electrode than could be elicited after recovery from anesthesia. In cat 47, in which the two electrodes were not placed on the sigmoid gyri (but on the lateral edge of the lateral gyrus, 16 mm. behind the cruciate sulcus), no response to stimulation could be obtained until the anesthesia had lessened considerably.

Such observations show that the anesthetic depresses or abolishes the excitability of structures in the cortex to electrical stimulation. Since facilitation of more or less remote points for a certain motion is abolished during anesthesia before the spot particularly associated with that motion loses its capacity to respond and since it has been shown that facilitation of distant points can be abolished by a shallow cut through the cortex between the facilitated spot and the spot primarily associated with the motion, it would appear that anesthesia blocks internuncial paths before abolishing the excitability of projection neurons, that is, if it is agreed that the ordinary responses from local parts of the motor area are obtained from stimulation of the pyramidal cells giving rise to projection fibers, as the work of Dusser de Barenne [10] indicated.

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9. Derbyshire, A. S.; Rempel, B.; Forbes, A., and Lambert, E. F.: The Effects of Anaesthetics on Action Potentials in the Cerebral Cortex of the Cat, Am. J. Physiol. **116**:577, 1936.

10. Dusser de Barenne, J. G.: The Disturbance After Laminar Thermocoagulation of the Motor Cerebral Cortex, Brain **57**:517, 1934.

In the normal animal, or in the anesthetized animal when the state of anesthesia remained constant, reduction in the quantity of response from a point could be obtained by weakening the strength of stimulus. Boynton and Hines [11] described this effect as a reciprocal of facilitation and termed it "centripetal individuation." A certain stimulus, for example, in an animal may provoke rhythmic flexion of both contralateral limbs, while a weaker stimulus may elicit only lifting of one limb (the limb the cortical center of which is nearest the electrode). Varying the length of application of a stimulus also affects the response, as a weak stimulus acting for a long time will facilitate wider areas of the cortex than when applied for a short time. The effects of varying the time, strength and frequency of the stimulus in animals prepared as in these experiments will form the subject of a subsequent report.

The interpretation of movements resulting from stimulation of points remote from the specific part of the motor area proved to be associated with the movments is not clear. In cats 43 and 47, for example, the electrodes were planted on the lateral gyrus 22 mm. and 16 mm., respectively, behind the cruciate sulcus. The movements obtained from these cats were similar to those obtained from stimuli applied in some regions of the motor area, but a period of summation of some length intervened between onset of the stimulus and that of the resulting motion. The explanation of the results of such stimulation may be that through short or long internuncial fibers the motor cortex on this side is activated, as in facilitation of points nearer the motor area, though we have never observed facilitation over such a distance in anesthetized animals.

Another possible explanation of the results obtained from points in the lateral gyrus may be that in some manner prolonged stimulation affects the projection fibers from the motor cortex which by degeneration experiments can be shown to run beneath this area—though this appears unlikely. Or the cortex stimulated may influence lower-lying nuclear masses which are concerned with these movements. In this connection, Cooper and Denny-Brown [4] remarked (page 233):

> Francois-Frank and Pitres obtained epileptiform after-discharge unaffected by removal of the cortical centers, and we regard this, as well as the close resemblance of clonic after-discharge to the well-known clonus in spinal mammalian preparation, as true indications that clonus and also probably faster dominant rhythms are features whose seat of origin is the spinal gray matter.

Tower and Hines [12] also obtained epileptiform attacks in monkeys by stimulation of various parts of the cortex after section of the pyramidal tracts.

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11. Boynton, E. P., and Hines, Marion: On the Question of Threshold in Stimulation of the Motor Cortex, Am. J. Physiol. **106**:175, 1933.

12. Tower, S. S., and Hines, M.: Dissociation of Pyramidal and Extrapyramidal Functions of Frontal Lobe, Science **82**:376 (Oct. 18) 1935.

Though rhythmic activity is possible from lower-lying centers, these experiments have served to emphasize the direct association of cortical areas with rhythmic activity of the extremities. Such an association was forecast by Ferrier [5] in his experiments. For example, in experiment 4 he observed that stimulation of a point just posterior to the cruciate sulcus caused a movement exactly like that "when a cat strikes a ball with its paw." After confirming this in experiment 5, he stated (page 47):

> After this stimulation the shoulder and limb continued for a minute or two to twitch in a choreic-like manner, the same movements being carried out, but in sporadic succession.

Ferrier used two electrodes with considerable distance between the points and so involved more cortex than a unipolar electrode, which may account for his obtaining this movement from areas back of the cruciate sulcus.

That different patterns of rhythmic movements may be obtained by stimulating different cortical areas might have been predicated from the work of Magoun, Ranson and Fisher,[13] who obtained rhythmic movements of the forelimb by stimulating the deeper portions of the cerebrum (bundles of projection fibers from cortical areas apparently). They said (page 6):

> The responses of the forelimb were usually rhythmically repeated and were always contralateral. The movements characteristically resembled stepping but sometimes suggested digging and at other times striking.

Similarly, Bard and Brooks [14] reported that stimulation applied to the dorsal surface of the exposed left caudate nucleus, when all the left cortex except that of the sigmoid gyri had been removed, provoked maximal flexion of the right hindleg, together with vigorous batting movements of the right foreleg. Whether the stimulus in this case affected the caudate nucleus or the descending projection fibers from the superimposed sigmoid gyri is questionable.

Perhaps the explanation of the rhythmic activity is expressed in the statement of Cooper and Denny-Brown (page 233 [4]):

> All the evidence is suggestive that the whole form of the response to stimulation of the motor cortex, and the clonic after-discharge characteristic of that

13. Magoun, H. W.; Ranson, S. W., and Fisher, C.: Corticifugal Pathways for Mastication, Lapping and Other Motor Functions in the Cat, Arch. Neurol. & Psychiat. **30**:292 (Aug.) 1933.

14. Bard, P., and Brooks, C. M.: Localized Cortical Control of Some Postural Reactions in the Cat and Rat Together with Evidence That Small Cortical Remnants May Function Normally, A. Research Nerv. & Ment. Dis., Proc. **13**: 107, 1932.

response, are the outward signs of a conflict of summated excitation and inhibition. This conflict, which is not obviously a feature of normal voluntary movement, is not unlikely the result of artificial provocation to concurrent activity of two naturally opposed groups of minute cells in the mosaic of the motor area. One of these groups produces excitation at the final motor neurone and the other inhibition. The inhibition so rapidly developed is not merely the expression of activity of the antagonist, indeed our double records show the resulting impedance in both antagonists at the same time. The inference from this we think is clear, that for a given movement the excitatory units and the inhibitory units lie microscopically intermingled in the cortex and, further, that representatives of movements in opposite directions are often closely enough related anatomically to be excited by the same stimulus.

In the intact animal, however, either with or without anesthesia, the rhythmic movements obtained from stimulating the "digging" or "batting" points are exceedingly like similar movements performed voluntarily and differ obviously from clonic movements that occur as after-effects of stimulation. It should be emphasized that rhythmic movements obtained from cortical stimulation require a relatively long stimulus, though no stronger than is necessary for simple movements. After-effects are the result usually of a stimulus of more than threshold strength or of one acting an excessive length of time.

That the placing reactions, which Bard and Brooks have shown to be disturbed or abolished by removal of the cortical motor area, are temporarily disturbed after the epileptic attacks resulting from stimulation is especially interesting in the light of the report of Notkin, Coombs and Pike [15] that in 94 per cent of a series of epileptic patients a positive Babinski sign was obtained after cessation of clonic movements. Further discussion of this will appear in the report of the epilepsies obtained in the present experiments.

The animals used in these experiments were friendly and tame, so that neither excitement nor restraint ordinarily interfered with the responses. The majority would lie or stand quietly while the stimuli were being applied and did not seem to mind the presence of the implanted electrodes or the extension wire used in stimulation. An extraneous influence introduced in the animals in which a coil was planted subcutaneously or inserted into the plug on the head was the slight vibration of the coil when activated by the primary. This produced a sensory stimulus that at times caused ducking the head and flattening the ears, even though the electrode touching the cortex had been dis-

15. Notkin, J.; Coombs, H. C., and Pike, F. H.: Clinical and Experimental Observations on the Babinski Reversal, Cardiovascular Reactions, Respiratory and Pupillary Changes During the Convulsive and Post-Convulsive Stages of General and Experimental Epilepsy, Am. J. Psychiat. **11**:679, 1932.

connected from the coil. Such stimuli interfered with the observations on movements of the head but were not present when the extension wire was used.

In cats stimulated by means of the extension cord, movements of the head were of great interest, since they were obtained from stimuli applied to widely separated points. There appeared to be primary movements (rotation and turning) of the head resulting from s .nulation of parts of the motor cortex, especially that near the presylvian gyrus (cats 33, 44, 50 and 51). In any of the cats movements of the head occurred in connection with stimuli which caused such great postural changes that the head was adjusted reflexly. Then there were movements of the head that appeared to be the results of an undesirable sensory stimulus, and the cat withdrew its head directly backward, not turning it to one side (cat 43).

In still other cats there was turning of the head that suggested an act of inquiry into something not unpleasant but at least unusual. This was noticed in cat 46 with the electrode near the occipital pole—the head was turned toward the contralateral side—and in cat 47, which turned its head and licked the contralateral side as if sensory stimuli were arising from the skin in that region.

Such movements as these and the ocular effects observed in cats 49 and 43 perhaps give evidence that stimulation affected sensory areas of the cortex primarily. These observations, however, would not agree with the map of sensory localization obtained by Dusser de Barenne [16] for the cat. Further work must be done before any definite remarks on the sensory effects can be made. There were evidences of sensory involvement during the epileptic attacks obtained with long or strong stimuli, but these were not primary effects. With the ordinary ranges of stimulation used, the cats experienced no painful stimulation. At times, however, when the stimulus was strong, it appeared that a slightly disagreeable sensation was set up which caused the cat to move its head as if attempting to withdraw it. Usually the cats appeared to enjoy the attention given them, and one especially friendly animal (cat 47) continued to purr while undergoing severe clonic after-effects of strong stimulation.

## SUMMARY AND CONCLUSIONS

By a method of permanently implanting electrodes on specific points of the cortex cerebri which allows recovery from anesthesia and the effects of operation, cortical points in cats were stimulated at intervals over long periods with and without anesthesia. The experiments demonstrate that the same response can be elicited from the same cortical

16. Dusser de Barenne, J. G.: Experimental Researches on Sensory Localizations in the Cerebral Cortex, Quart. J. Exper. Physiol. **9**:355, 1916.

point from day to day and argue against any marked instability of cortical points except under the temporary influence of transient physiologic states.

The influence of an anesthetic on the response to repeated stimulation of a cortical point appears to be expressed by the depression or elimination of the effects (of facilitation) on neighboring cortical areas before the depression or abolition of the response from the point under the electrode. The picture is similar to that obtained in the responses to successively weaker stimuli applied to the same point.

No evidence of pain as a primary response to cortical stimulation was observed, though some evidence of sensory effects was found.

The method allows the production of epileptiform seizures at will in the "normal" animal.

# PHENYLPYRUVIC OLIGOPHRENIA

## INTRODUCTORY STUDY OF FIFTY CASES OF MENTAL DEFICIENCY ASSOCIATED WITH EXCRETION OF PHENYLPYRUVIC ACID

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In the study of the so-called primary, or endogenous, mental deficiency, when one excludes well defined pathologic types, such as amaurotic idiocy, tuberous sclerosis and mongolism, a large number of cases may still be found that escape any but a psychometric classification. It can hardly be doubted that these cases constitute a heterogeneous group in which future investigation will individuate new nosologic types, differing essentially in etiology, symptomatology and pathologic character.

An apparently new type of mental deficiency has recently been indicated by Fölling,[1] with the term "imbecillitas phenylpyruvica." This author reported having found phenylpyruvic acid in the urine of 10 mentally defective patients, 4 of whom were males and 6 females, ranging from 2 to 20 years of age. In 6 instances the metabolic abnormality was present in two members of a sibship, but it was never found to occur in mentally normal relatives. The mental defect was generally of a marked degree, and in the majority of cases muscular rigidity was observed, ranging from simple hyperactivity of the tendon reflexes to spastic paraparesis.

Since the commencement of the present investigation, Penrose[2] has published a brief clinical note describing 2 new cases, in siblings, and a pedigree[3] in a third case, with a discussion of the genetic data.

### MATERIAL

The present introductory study comprises 50 cases of phenylpyruvic oligophrenia,[4] all of which were studied personally. Twenty-one patients were inmates

From the Research Department, Letchworth Village.

1. Fölling, A.: Ueber Ausscheidung von Phenylbrenztraubensäure in den Harn als Stoffwechselanomalie in Verbindung mit Imbezillität, Ztschr. f. physiol. Chem. **227**:169, 1934.

2. Penrose, L. S.: Two Cases of Phenylpyruvic Amentia (Phenylketonuria), Lancet **1**:23 (Jan. 5) 1935.

3. Penrose, L. S.: Inheritance of Phenylpyruvic Amentia, Lancet **2**:192 (July 27) 1935.

4. The term "phenylpyruvic oligophrenia" has been preferred to that of "phenylpyruvic amentia," used by Penrose, following in this the official English

*(Footnote continued on next page)*

at Letchworth Village; 13 patients were examined at the Wassaic State School and 8 at the Rome State School.[5] Eight more persons, siblings of institutionalized patients, were examined at their respective homes. In the genetic study 12 more cases were taken into account, in which the patients died prior to the undertaking of the present study; the persons were siblings of patients under study, and the clinical manifestations strongly suggest that they belonged to the same group, although examination of the urine was lacking.

Examination of the members of the family of 35 patients showed that phenylpyruvic acid did not in any instance occur in the urine of mentally normal members. That phenylpyruvic acid is never found in the urine of normal persons or in the most varied pathologic conditions may be indirectly assumed from the fact that in the test for phenylpyruvic acid the same reagent (ferric chloride) is used as that in Gerhardt's test for diacetic acid and in Obermeyer's reaction for indican; in several years of personal examinations of urine as a routine, involving many thousand samples, the green color characteristic of the reaction for phenylpyruvic acid was never observed.

## CLINICAL CONSIDERATIONS

*Incidence.*—Eight thousand and forty-three inmates, representing all forms and degrees of mental deficiency, were examined; 4,245 of these were males and 3,798 females. Forty-two patients were found to have phenylpyruvic acid in the urine in addition to a peculiar clinical syndrome, dominated by mental deficiency. This gives a percentage of 0.522 of patients with Fölling's disease among institutionalized mentally defective persons.

If one assumes that feebleminded persons constitute 0.8 per cent of the general population (British Deficiency Committee, 1929) the incidence of phenylpyruvic oligophrenia in the general population should be 0.004 per cent, i. e., 1 in 25,000. The disease is therefore rare and shows a frequency similar to that of other inborn errors of metabolism, e. g., cystinuria (1 in 20,000).

*Race.*—The distribution of the patients according to race is shown in table 1. It will be noted that the Jewish race, although constituting 20 per cent of inmates of institutions for mentally defective persons in New York City, was not represented in our group of patients. Noteworthy also is the fact that none of the patients belonged to the

classification of the Royal Medico-Psychological Association, which avoids the term "amentia" but uses the term "oligophrenia" for all forms of mental defect. The term "imbecility," employed by Fölling, is generally used in the United States to designate a circumscribed group of mental defectives, i. e., persons with feebleminedness ranging from an intelligence quotient of 20 to one of 50. The term is therefore misleading here, since a large percentage of patients showed an intelligence quotient below 20.

5. Dr. H. C. Storrs and Dr. Charles Bernstein, the respective superintendents of the two institutions last mentioned, gave permission to examine their patients and to use their laboratory facilities.

African race. Otherwise, the figures fail to show any important variation in racial susceptibility to the disease.

*Sex.*—Thirty patients were females and 20 males. The ratio of affected males to affected females is therefore 2:3. However, 4,245 males were examined, as compared with 3,788 females, so that the ratio of affected males should be considered slightly below the figure 2:3. Thirteen families in which 2 or more affected siblings were present offered data for the determination of the ratio of affected males to affected females as compared with that of normal males to normal females in the sibship. The first ratio was 3:5, whereas the second was 7:5. Thus, the excess of females with Fölling's disease corresponds to an excess of normal males in the same sibship, so that in

TABLE 1.—*Distribution of Patients According to Race*

| Race | Number of Patients | Percentage | Percentage of Mentally Defective Patients |
|---|---|---|---|
| Irish | 12 | 24 | 9 |
| Italian | 12 | 24 | 18 |
| Slavonic | 3 | 6 | 3.5 |
| Dutch | 3 | 6 | 1 |
| English | 3 | 6 | 7 |
| German | 2 | 4 | 5 |
| Scandinavian | 1 | 2 | 1 |
| Jewish | 0 | 0 | 20 |
| African | 0 | 0 | 12 |
| Mixed | 13 | 26 | 20 |

* The figures are based on data on 1,000 patients at Letchworth Village, for whom details concerning three generations were available.

both single cases and sibships the excess of affected females over affected males seems well established.

*Age.*—The ages of the patients varied from 2 to 58 years, with an average of 21 (10 per cent of the patients were in the first decade of life, 46 per cent in the second, 26 per cent between the ages of 20 and 30 and 12 per cent between the ages of 30 and 40). Only 2 patients were over 40. These figures, however, cannot be considered as indicative of any discrimination based on age, since the large majority of the 8,000 patients examined were between 5 and 25 years of age.

As to the age of onset, although in no case has the condition been diagnosed at birth, there is sufficient indication that it is congenital.

*Etiology.*—Maternal Health: Details as to the maternal health during pregnancy were obtained in 70 per cent of the cases: In no more than 4 instances was there a history of pregnancy complicated by frequent vomiting and physical deterioration. Toxic, infectious or deficiency factors acting on the child during intra-uterine life seem, therefore, improbable.

Trauma at Birth: This is also to be excluded as a factor in the etiology; in only 3 cases was there a history of instrumental delivery, and in these instances the parents were definite in the statement that the procedure did not apparently injure the child. In none of the cases was there a history of asphyxia at birth. None of the patients were born prematurely.

Infectious Diseases: Infectious disease occurred in early childhood in 4 cases, with a symptomatology suggesting cerebral complication; in these cases, however, the details were unsatisfactory, and it may be noted in particular that there was no conclusive evidence as to whether the mental defect was anterior to or dated from the occurrence of the infectious disease. On the other hand, it was often pointed out by the parents that the child had never had any disease important enough, in their opinion, to account for the mental deficiency. As a matter of fact, the personal history in the whole series shows a striking resemblance, being characterized by normal physical development, in contrast to the mental retardation obvious in early infancy.

Syphilis: Clinical and serologic evidence of parental syphilis was lacking in the whole series of cases, although in 2 instances syphilis was suspected in the father. In these cases, however, the Wassermann test was performed repeatedly and always gave a negative reaction, and clinical signs of the disease were not demonstrated on physical examination. Moreover, all but 4 of the patients were submitted to a Wassermann test of the blood, with constantly negative results. In 30 patients the spinal fluid was also examined: The test for globulin and the Wassermann and colloidal gold tests always gave negative results. Therefore, syphilis as a factor in the etiology of the disease seems thus far to be excluded.

Disturbances of the Endocrine Glands: One patient showed increase of subcutaneous fat, with a distribution suggesting that seen in the Fröhlich type, and roentgenologically the sella appeared smaller than normal. Another patient showed facial features recalling the mongolian facies, although no other signs of mongolism were observed. Altogether, evidence to suggest endocrine imbalance as a factor in the causation of the disease was lacking, as far as common clinical symptoms and signs were concerned. More detailed investigations of the endocrine system are under study.

Other factors of possible importance in the etiology are the place of the patient in the order of birth and the age of the parents at the time of conception.

Table 2 shows the ordinal position in the family of the affected children. The figures comprise all the cases included in the genetic study. The expected number for each ordinal place was calculated according

to the method of Greenwood and Yule.[6] Except for the figures in the fourth ordinal position, the agreement between the observed and the expected values is sufficiently satisfactory to assume that the ordinal place in the family, more particularly primogeniture, appears to have no etiologic significance.

The age of the parents at the time of conception was known exactly in 42 instances. The age of the mother varied from 19 to 42, with an average of 28.2, and that of the father from 21 to 50, with an average of 31.8. No obvious disparity was observed between the ages of the parents. These figures, when compared with those given by van der Scheer [7] for normal children (average maternal age, 31.2; average paternal age, 33.8), seem to exclude any relation of paternal age and maternal exhaustion to the incidence of the disease.

TABLE 2.—*Ordinal Position in the Family of Children with Phenylpyruvic Oligophrenia*

| Ordinal Position | Size of Sibship (s) | | | | | | | | | | | | Observed Total Number | Expected Total Number |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | | |
| 1 | 2 | 5 | 2 | 3 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 15 | 16.08 |
| 2 | .. | 5 | 4 | 3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 13 | 14.08 |
| 3 | .. | .. | 3 | 0 | 1 | 3 | 0 | 1 | 1 | 1 | 0 | 1 | 11 | 9.08 |
| 4 | .. | .. | .. | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 15 | 6.08 |
| 5 | .. | .. | .. | .. | 1 | 2 | 1 | 0 | 0 | 0 | 0 | 1 | 5 | 4.08 |
| 6 | .. | .. | .. | .. | .. | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 5 | 4.02 |
| 7 | .. | .. | .. | .. | .. | .. | 2 | 0 | 1 | 0 | 0 | 0 | 3 | 2.69 |
| 8 | .. | .. | .. | .. | .. | .. | .. | 0 | 0 | 0 | 0 | 0 | 0 | 1.84 |
| 9 | .. | .. | .. | .. | .. | .. | .. | .. | 0 | 0 | 0 | 0 | 0 | 1.47 |
| 10 | .. | .. | .. | .. | .. | .. | .. | .. | .. | 0 | 0 | 1 | 1 | 1.25 |
| 11 | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | 0 | 1 | 1 | 1.05 |
| 12 | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | 0 | 0 | 0.87 |
| Total $n_s$* | 2 | 10 | 9 | 8 | 3 | 8 | 6 | 3 | 2 | 2 | 2 | 4 | 59 | 62.59 |
| $n_s/s$..... | 2 | 5 | 3 | 2 | 0.6 | 1.33 | 0.85 | 0.37 | 0.22 | 0.2 | 0.18 | 0.33 | | |

* In the table $n_s$ indicates the number of affected sibs in a sibship of a given size.

In conclusion, it may be said that a critical analysis of the personal history of the patients makes it improbable that factors due to external environment play a significant rôle in the causation of the disease.

## GENETIC BEHAVIOR [8]

The present series comprises 37 families, with a total number of 176 siblings. The total number of affected children was 59; 47 were

6. Greenwood, M., and Yule, G.: On the Determination of Size of Family and of the Distribution of Characters in Order of Birth from Samples Taken Through Members of the Sibships, J. Roy. Statist. Soc. **77**:179, 1914.

7. van der Scheer, W.: Beiträge zur Kenntnis der mongoloiden Missbildung (Mongolismus), Berlin, S. Karger, 1927.

8. Dr. Charles B. Davenport, director of the department of genetics, the Carnegie Institution of Washington, reviewed this section and offered valuable suggestions.

studied personally, and for the other 12 children, who died prior to the present investigation, clinical data were available. In 3 cases studied personally no family history could be obtained.

In 18 families 2 or more members of the sibship were likewise affected, giving a total of 40 familial cases, i. e., 67.8 per cent.

In all the familial cases and in about 70 per cent of the sporadic, the living parents were examined personally; in the whole series they were found to be mentally normal, and the test for phenylpyruvic acid in the urine gave negative results, except in 1 instance. This woman, an imbecile aged 34, had 4 children, 2 of whom were normal and 2 affected, being inmates of an institution. A second possible transmission of the disease from parent to child was offered by a patient of the present series, a girl of low grade intelligence, who had borne an illegitimate boy. This child was an idiot with marked motor disability, who died at 5 years of age. From the clinical data available, there is good basis for inferring that he was affected by the same disease as the mother.

The grandparents could be examined in only a few instances, whereas in numerous cases uncles, aunts and cousins were examined. The results were always normal.

Consanguinity between the parents was noted in 3 families, with a total of 7 affected children. In 24 families the parents were not related, and in 10 families no definite information on this point could be obtained.

The raw percentage of the phenotypes in the 35 families examined ($\Sigma n_s$ being the number of the siblings and $\Sigma t_s$ the number of the children affected) is determined as follows:

$$100 \frac{\Sigma t_s}{\Sigma n_s} = 100 \frac{59}{176} = 33.5 \text{ per cent}$$

Factorial analysis of the material based on the recessive gene hypothesis and calculated according to Hogben[9] is shown in table 3, in which s is the size of the sibship, $n_s$ the number of sibships with a given number of sibs, $\Sigma n_s$ the sum of the number of sibs in these sibships and $t_s$ the observed number of siblings affected. The number of affected siblings ($r_s$) that one might expect to observe is calculated according to the formula:

$$r_s = n_s p c_s, \text{ in which } c_s = \frac{s}{1 - q^s} \text{ and } q = (1 - p),$$

p being the theoretical expectation of affected offspring, i. e., one-fourth (on the basis of the theory of monorecessive genes). The standard error is $\mp \sqrt{\Sigma n_s k_s}$, in which $k_s = \frac{s(1-q)}{(1-q^s)^2} \times [sq^s (q-1) + q(1-q^s)]$.

The correspondence between the observed number of affected children and the expectation on the basis of the recessive mendelian hypothesis is satisfactory, the total difference being —1.88, with a standard error of ± 4.69.

9. Hogben, L.: The Factorial Analysis of Small Families with Parents of Undetermined Genotype, J. Genetics **26**:75, 1932.

In table 4 the material is presented according to Weinberg's[10] "sib method," s being the number of siblings in a family, t the number of affected children, t(s —1) the siblings of affected children and t(t —1) the affected siblings of the affected children. The standard error is $\pm \frac{\sqrt{P\,(100 - P)}}{s}$, in which $P = 100\ \frac{\Sigma\, t\,(t-1)}{\Sigma\, t\,(s-1)}$

The percentage of affected children, $100\,\frac{t\,(t\text{-}1)}{t\,(s\text{-}1)}$, is therefore 20.85. Since the standard error is $\pm$ 3.18-, the figure 24.03 per cent may be inferred, which is satisfactory on the basis of the recessive mendelian hypothesis.

In commenting on the genetic data, it may be stated first that a genetic mechanism is responsible for the condition, as indicated by the high percentage (67.8) of familial cases; in fact, the condition being rare, the element of mere chance may be readily excluded in the explanation of familial occurrence.

TABLE 3.—*Factorial Analysis of Material According to Hogben's Method*[9]

| s | $n_s$ | $\Sigma ns$ | $t_s$ | $r_s$ | $n_s k_s$ |
|---|---|---|---|---|---|
| 1 | 2 | 2 | 2 | 2.00 | 0.00 |
| 2 | 8 | 16 | 10 | 9.19 | 1.18 |
| 3 | 7 | 21 | 9 | 9.16 | 1.83 |
| 4 | 5 | 20 | 8 | 7.31 | 2.09 |
| 5 | 1 | 5 | 3 | 1.64 | 0.51 |
| 6 | 4 | 24 | 8 | 7.39 | 2.99 |
| 7 | 3 | 21 | 6 | 6.17 | 2.91 |
| 8 | 2 | 16 | 3 | 4.46 | 2.32 |
| 9 | 2 | 18 | 2 | 4.88 | 2.77 |
| 10 | 1 | 10 | 2 | 2.64 | 1.65 |
| 11 | 1 | 11 | 2 | 2.87 | 1.80 |
| 12 | 1 | 12 | 4 | 3.07 | 2.01 |
| Total | 37 | 176 | 59 | 60.88 | 22.06 |

The frequent occurrence of the condition among several members of the same sibship and its absence in the majority of the parents suggest that the disease may be due to a rare recessive gene substitution.

As is well known, when a disease behaves genetically as a rare mendelian recessive character, a recessive homozygous person is, with rare exception, the offspring of heterozygous parents; in other words, he is due mainly to the combination DR $\times$ DR: Therefore, in a sibship in which one person shows a recessively determined trait, 25 per cent of the sibs would show the same trait, i. e., the classic mendelian ratio of one-fourth affected to three-fourths normal offspring is theoretically to be expected.

In the present material a raw percentage yields a figure (33.5) which is, as usual, too high to fall in the theoretical 25 per cent characteristic of a mendelian recessive trait. However, critical elaboration

10. Weinberg, W.: Methoden und Technik der Statistik mit besonderer Berücksichtigung der Sozialbiologie, in Gottstein, A.; Schlossman, A., and Teleky, L.: Handbuch der sozialen Hygiene und Gesundheitsfürsorge, Berlin, Julius Springer, 1925.

by two different statistical methods indicates completely satisfactory agreement between expectation and observation. The percentage observed with Hogben's method is 24.22. The same percentage is obtained with Bernstein's [11] a priori method, of which Hogben's method is a derivation. These figures, when corrected, give evidence of striking agreement with the classic mendelian ratio. A completely different procedure, Weinberg's sib method, although yielding a slightly lower percentage, is also satisfactory. There is, therefore, statistical justification

TABLE 4.—*Analysis of Material According to Weinberg's Method* [10]

| Family | s | t | t (s − 1) | t (t − 1) |
|---|---|---|---|---|
| 1 | 7 | 2 | 12 | 2 |
| 2 | 2 | 2 | 2 | 2 |
| 3 | 4 | 2 | 6 | 2 |
| 4 | 1 | 1 | 0 | 0 |
| 5 | 11 | 2 | 20 | 2 |
| 6 | 7 | 2 | 12 | 2 |
| 7 | 2 | 2 | 2 | 2 |
| 8 | 4 | 2 | 6 | 2 |
| 9 | 10 | 2 | 18 | 2 |
| 10 | 3 | 1 | 2 | 0 |
| 11 | 2 | 1 | 1 | 0 |
| 12 | 3 | 1 | 2 | 0 |
| 13 | 2 | 1 | 1 | 0 |
| 14 | 3 | 1 | 2 | 0 |
| 15 | 6 | 2 | 10 | 2 |
| 16 | 12 | 4 | 44 | 12 |
| 17 | 9 | 1 | 8 | 0 |
| 18 | 7 | 2 | 12 | 2 |
| 19 | 4 | 1 | 3 | 0 |
| 20 | 2 | 1 | 1 | 0 |
| 21 | 6 | 1 | 5 | 0 |
| 22 | 3 | 1 | 2 | 0 |
| 23 | 6 | 3 | 15 | 6 |
| 24 | 2 | 1 | 1 | 0 |
| 25 | 4 | 1 | 3 | 0 |
| 26 | 9 | 1 | 8 | 0 |
| 27 | 3 | 2 | 4 | 2 |
| 28 | 3 | 2 | 4 | 2 |
| 29 | 4 | 2 | 6 | 2 |
| 30 | 6 | 2 | 10 | 2 |
| 31 | 8 | 1 | 7 | 0 |
| 32 | 2 | 1 | 1 | 0 |
| 33 | 5 | 3 | 12 | 6 |
| 34 | 8 | 2 | 14 | 2 |
| 35 | 2 | 1 | 1 | 0 |
| 36 | 1 | 1 | 0 | 0 |
| 37 | 3 | 1 | 2 | 0 |
| Total | 176 | 59 | 259 | 54 |

for regarding the condition as determined by a single recessive gene substitution.

Additional evidence is afforded in the following findings:

In 3 instances consanguinity of the parents could be detected; although the number is small, the incidence may be considered to be significantly higher than that in the general population. As Lenz [12]

11. Bernstein, F.: Variationen und Erblichkeitsstatistik, in Hartmann, M.: Handbuch der Vererbungswissenschaft, Berlin, Verlagsbuchhandlung Gebrüder Borntraeger, 1929.

12. Lenz, F.: Die Bedeutung der statistisch ermittelten Belastung mit Blutsverwandtschaft der Eltern, München. med. Wchnschr. **66**:1340, 1919.

pointed out, when a rare disease is due to a recessive gene, it occurs more frequently among offspring of consanguineous parents, a constant relation existing between the frequency of affected offspring of consanguineous unions and the absolute incidence in the general population of the rare disease recessively determined. Moreover, as Dahlberg [13] has demonstrated, the frequency of consanguinity of parents suggests the monohybrid type of recessive behavior, whereas consanguinity is to be expected less frequently in dihybrid and still less frequently in polyhybrid recessivity.

In 2 instances a recessive person had borne children; in 1 case there was 1 child, who was probably affected; in the other case 4 children were present, 2 of whom were affected and 2 normal; in other words, 50 per cent of the offspring exhibited the character, as is to be expected in the case of recessive heredity in which a single gene is involved as the result of a mating of an affected with a heterozygous person.

In 3 instances half-siblings of an affected subject were present, none of these exhibiting the character, as is to be expected when the disease is due to a rare recessive gene; in fact, both parents being heterozygous and the gene being rare, it is highly improbable that one of the parents would marry again a heterozygous person (Rudin [14]).

In all cases but 1 (or possibly 2) the parents did not exhibit the character; this seems to exclude the intervention of two complementary dominant genes; the familial incidence of a condition determined by two dominant genes is, in fact, practically the same as that for a single recessive gene substitution (Hogben [15]). The two cases can always be distinguished, if the condition is not lethal, by the high proportion in the first instance of affected persons with affected offspring.

Finally, the observation seems important that within a family the disease was clearcut in the majority of cases, so that the distinction between affected and normal siblings was strikingly abrupt. This sharp segregation is a good additional criterion for regarding a trait as determined by a single gene (Penrose [16]).

In conclusion, this genetic study provides an exceptional illustration of a single recessive gene substitution in a definite clinical type of endogenous mental deficiency.

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13. Dahlberg, G.: Inzucht bei Polyhybridität beim Menschen, Hereditas **14**: 83, 1930.

14. Rudin, E.: Zur Vererbung und Neuentstehung der Dementia praecox, Berlin, Julius Springer, 1916.

15. Hogben, L.: The Genetic Analysis of Familial Traits: Single Gene Substitutions, J. Genetics **25**:97, 1931.

16. Penrose, L. S.: The Influence of Heredity on Disease, London, H. K. Lewis & Co., Ltd., 1934.

That a rare recessive gene is responsible for amaurotic idiocy in both the juvenile and the infantile form has been proved by Sjögren [17] and Slome;[18] the present investigation confirms an assumption of Penrose [3] that other forms of mental deficiency, in particular phenylpyruvic oligophrenia, are recessively determined.

## SYMPTOMATOLOGY

The majority of the patients of the present series showed a fairly well defined constitutional type.

The stature was within normal limits; the different segments of the body were harmoniously developed and the features of the face regular and often attractive, in contrast to the misproportioned bodily structures and distorted features which taint the majority of idiots and imbeciles. The blond type largely predominated (86 per cent of the patients), coexisting generally with blue eyes (66 per cent) and pale, delicate skin. A striking example was offered by an attractive idiot baby with blond hair and blue eyes, who belonged to a family of Sicilian extraction, all the members of which, for at least three generations, were of a very dark Mediterranean race, as evidenced by personal examination and numerous photographs.

Complete anthropologic measurements were obtained in 18 patients. Only the craniometric data showed deviation from the normal. The mean of 14 indexes of cranial capacity, computed according to the formula of Lee and Pearson, in patients above 20 years of age, was 1,303.35 and the range of variation narrow, extending from 1,134 to 1,449. The patients are therefore to be considered slightly microcephalic.

General systemic examination failed to show any abnormality of the thoracic and abdominal organs, but in the majority of cases acrocyanosis was observed to denote a vegetative disorder.

Although more detailed endocrinologic investigations are under way, common physical signs of endocrinal imbalance were not observed. In adult patients the genitalia were of normal appearance, and secondary sexual characters appeared to be normally developed. Puberty, though generally retarded, had been normal. The menses were regular. One patient, although affected by a severe form of idiocy, had normally borne a child.

In about half the cases lesions of the skin were observed, consisting of more or less diffuse patches of eczema. One patient showed chronic eczema diffusely distributed over the whole surface of the body, with particular resistance to any kind of treatment. In 2 other patients a similar type of eczema, lasting over two years, was recorded in the history. Moreover, the cause of death of 1 patient was recorded on the death card of the hospital as generalized severe eczema. Another patient showed typical patches of psoriasis.

The relationship of the cutaneous lesions to the metabolic error remains undetermined; it will be noted that numerous patients showed erythema when exposed to the sun for short periods. However, no abnormal pigmentations of the skin were noted.

*Neurologic Manifestations.*—These changes are a characteristic component of the disease. In a few patients, showing an intelligence quotient above 40,

17. Sjögren, T.: Die juvenile amaurotische Idiotie, Hereditas **14**:197, 1931.

18. Slome, D.: The Genetic Basis of Amaurotic Family Idiocy, J. Genetics **27**:363, 1933.

neurologic examination gave normal results; however, definite hyperactivity of the deep reflexes betrayed involvement of the central nervous system.

In the majority of cases anomalies, particularly of the motor system, were demonstrable. It will be noted that the motor system is the most easily examined in idiotic patients, in whom the marked mental defect precludes cooperation.

The posture of the patients was often that of general flexion, with bent head and body. The upper extremities when at rest were bent at the elbows and wrists. This characteristic flexed attitude was also observed in the lower extremities, when the patients lay in bed. The gait generally consisted of short steps; the body was held rigidly forward, and the usual associated movements of the trunk, arms and head were scanty, retropulsion and anteropulsion being observed occasionally. In more than half the cases these disorders of posture and gait were observed; their frequency increased with the lower mental levels.

Muscular strength appeared fairly well preserved in all cases, as far as accurate testing was possible. No definite local paresis was detected in any case; some of the younger patients, including a girl 9 years of age, were unable to walk. Examination of the motility of the lower extremities, however, showed normal crude strength of the muscles; so inability to walk had to be referred to the low mental age. Signs of muscular atrophy or wasting were not observed.

In 70 per cent of cases definite increase in the muscular tone was detected. The rigidity involved both flexor and extensor muscles and remained the same throughout the whole range of movements. At times cogwheel movements were produced by passive motion of the upper extremities. In 5 cases actual muscular catatonia was demonstrated.

In all cases the deep reflexes were active, and the response was often diffuse, particularly for the radial and patellar reflexes. Transient or permanent clonus of the foot and rotula was detected in 34 per cent of the cases. In all cases the superficial and, in particular, the abdominal reflexes were unimpaired. A clear Babinski sign was observed in only 1 case; a woman aged 58 showed signs of precocious senility, so that the possibility of a complicating senile condition of the brain was suggested. In all other cases neither the Babinski nor any other sign of pyramidal involvement was elicited. Among other abnormal reflexes, Piotrowski's sign was present in a high percentage of cases and was generally marked; at times other signs of the so-called extrapyramidal series were detected (Rossolimo, Pussep and Schijver-Bernhard).

Hyperkinetic manifestations were observed in 66 per cent of the cases. The most frequently encountered hyperkinesis was tremor of the unsupported stretched hands, the movements being rhythmic, of small amplitude and at a rate of from 150 to 180 per minute. Fatigue and emotional stress seemed at times to accentuate the tremor.

Typical athetosic movements of the hands were observed in several cases; more frequently the athetosic manifestations were combined with movements of a choreiform character.

Accurate investigations of sensibility were possible only in patients of high grade in whom both special senses and cutaneous sensations appeared normal.

Definite signs of cerebellar involvement never occurred. Equilibratory coordination seemed unimpaired. Examination of the cranial nerves failed to reveal any abnormality.

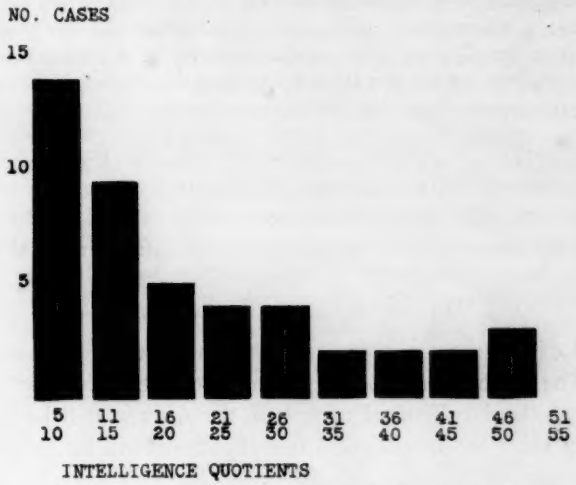
In 6 patients convulsive seizures had occurred during infancy. These attacks had always been few and had the usual characteristics of grand mal.

The spinal fluid was examined in 25 cases; the amount of protein was normal, and the reactions of Pandy, Nonne, Noguchi and Weichbrodt were negative. The

Wassermann reaction was also constantly negative, and in no case was there increase in the number of cells. In 8 cases in which examination of the spinal fluid was performed for phenols, total nitrogen and nonprotein and protein nitrogen, the figures obtained failed to show deviation from the normal. Phenylpyruvic acid was constantly absent from the spinal fluid.

Encephalograms were made in 11 cases. In several instances the lateral ventricles appeared to be moderately but clearly dilated, and diffuse increase of subarachnoid air could be detected. There is, therefore, justification for a roentgenologic diagnosis of diffuse cortical atrophy. Other signs of intracranial pathologic change were not detected.

Altogether, the neurologic manifestations may be regarded mainly as an extrapyramidal syndrome. Although lack of pathologic control makes difficult any anatomicoclinical correlation, it appears from examination of encephalograms that the extrapyramidal signs may be referred simply to cortical atrophy particularly




Graph 1.—Intelligence quotients of 45 patients.

of the frontal lobe, in accordance with the theoretical connection between lesion of the frontal lobe and symptoms and signs of the so-called extrapyramidal series. The hyperactivity of the deep reflexes would then be easily interpreted as lack of cortical control.

*Psychologic Manifestations.*—Pronounced intellectual defect was present in all cases. Forty-five patients were submitted to psychometric measurements, the Stanford revision of the Binet-Simon test being used as a routine, with the Kuhlmann-Binet test for persons of the lower levels of intelligence. The results expressed in terms of the intelligence quotient are shown in graph 1, from which it can be seen that the series comprised 28 (71 per cent) idiots, i. e., persons with an intelligence quotient below 20, and 17 (29 per cent) imbeciles with an intelligence quotient between 20 and 50.

The intellectual defect showed unquestionably the characteristic of failure of development and not that of disintegration of developed mentality. In the whole

series mental defect was obvious during the first year or, at most, by the second year. In only 2 cases did there seem to be normal development of mentality during the first year, followed by progressive deterioration, but in both these cases the available data were too uncertain and unreliable to warrant any conclusion. It seems, however, that in a certain number of cases slow mental deterioration of an already low mentality may occur in successive years, as was evidenced in 3 cases in which successive psychometric examinations were available. In 10 other cases successive examinations failed to reveal any changes of mental level.

In a few of the patients of low grade intelligence stereotyped bizarre movements occurred, such as elaborate play with the hands and fingers; one patient bumped her head against the wall so frequently that a large patch of alopecia had resulted. In 2 cases definite emotional unbalance was noted, consisting of expressive movements of fear and anxiety, the psychologic content of which could not be assessed, owing to the low mentality of the patients. Two other patients were mischievous and destructive, constituting difficult behavior problems. In general, however, the patients were apathetic, showing no indication of joy or anger; they were at times semistuporous, slow in motor activities and easily managed. In several instances peculiarities were noted, consisting of a tendency to reiteration either of movements or of words and sentences. In these cases echolalia and occasionally echopraxia were also observed.

In summary, the clinical manifestations, in their constitutional, neurologic and psychologic aspects, appear to occur with a certain constancy and are sufficiently characteristic to afford justification for regarding them as constituting a fairly well defined clinical syndrome.

## BIOCHEMICAL OBSERVATIONS

Several of the most cooperative patients were subjects of metabolic studies. The experiments being incomplete, the following report and discussion of the biochemical aspect of the disease will be limited. A detailed report of the biochemical investigations will be published later.

*Methods.*—The presence of phenylpyruvic acid in the urine is easily detected, owing to its color reactions. The addition of a few drops of a 5 per cent solution of ferric chloride yields a dark green color, which gradually disappears in a few minutes. The urine must be acid; it is necessary to acidify alkaline urine, preferably with a few drops of diluted sulfuric acid.

A second color reaction is obtained by addition to the alkalized urine of trinitrophenol; an orange-red color results. Previous treatment with Lloyd's reagent (a specially prepared siliceous earth) is necessary in order to remove creatinine, which gives the same color reaction.

Phenylpyruvic acid was isolated from the urine in its crystalline form, according to the method indicated by Fölling.[1] This somewhat long procedure, however, yields a very small amount of acid. A larger quantity may be obtained by a simpler method: The urine, after it was shaken with Lloyd's reagent, was acidified with hydrochloric acid, saturated with sodium chloride and extracted with ether in a Kutscher-Stendel apparatus. In the flask containing ether a few cubic centimeters of a solution of sodium ethylate was added, in order to obtain the sodium salt of phenylpyruvic acid. This salt, being insoluble in alcohol, was

easily recovered after evaporation of the ether and was purified by washing several times with alcohol. Loss of phenylpyruvic acid, which is rapidly oxidized, was thus avoided, the salt being a stable compound. Pure acid may be obtained easily from the sodium phenylpyruvate by the procedure of Hemmerlé.[19]

It was found convenient, in order to recover larger amounts of the acid, to isolate it from a large quantity of urine as a lead salt and to extract the acid with ether in successive stages.

Isolation of phenylpyruvic acid was also attempted, on the basis of the property of the ketone radical of the acid to form semicarbazone. The procedure followed the lines suggested by Chandler and Lewis.[20] However, though semicarbazone was easily formed with pure phenylpyruvic acid, it was obtained inconsistently from the urine. This failure might be explained by assuming that phenylpyruvic acid easily acquires an enolic form (Hemmerlé[19]).

Quantitative determination of phenylpyruvic acid in urine was obtained with a titration method. The compound was oxidized by boiling the urine, shaken with Lloyd's reagent and strongly acidified, with an oxidizing agent (generally sodium bichromate), and the resulting total benzoic acid (free and combined) was extracted with chloroform and titrated with sodium ethylate. The procedure followed the modification by Kingsbury and Swanson[21] of the method of Folin and Flanders[22] for the determination of hippuric acid. This last acid was previously eliminated by precipitation. The method was tested with pure phenylpyruvic acid prepared according to Hemmerlé[19] and found to give from 80 to 85 per cent of recovery, which was considered satisfactory.

Attempts to develop a quantitative colorimetric technic failed. The green color reaction characteristic of phenylpyruvic acid could not be used because it fades rapidly. The orange color reaction was more constant, and a method was therefore developed based on Folin's colorimetric method for the determination of creatinine. This last was eliminated with Lloyd's reagent and a standard solution of phenylpyruvic acid was prepared from the pure product. This rapid and simple method was used in several series of experiments, but it was later found that the color was interfered with by substances other than phenylpyruvic acid and creatinine.

*Vehicles of Excretion.*—Urine appeared to be the only vehicle of excretion of phenylpyruvic acid. The ether extract of feces failed to show the acid, even after twenty-four hours of continuous extraction. The reaction of the blood serum to ferric chloride was negative, but after extraction of 100 cc. of blood the ether showed a positive reaction; the compound is therefore present in the blood, though in small quantity. Attempts to detect the acid in the spinal fluid failed, even after continuous extraction of 100 cc. of fluid.

In the whole series of experiments, the total nitrogen, creatinine, creatine and phenols (total and free) were determined in each sample of urine. Of these phenols showed deviation from the normal, the figures being twice or three

19. Hemmerlé, R.: Sur l'acide phenylpyruvique, Ann. de chem. **7**:226, 1917.

20. Chandler, J. P., and Lewis, H. B.: Comparative Studies of the Metabolism of the Amino-Acids: The Oxidation of Phenylalanine and Phenylpyruvic Acid in the Organism of the Rabbit, J. Biol. Chem. **96**:619, 1932.

21. Kingsbury, F., and Swanson, W.: A Rapid Method for the Determination of Hippuric Acid in Urine, J. Biol. Chem. **48**:13, 1921.

22. Folin, O., and Flanders, F.: A New Method for the Determination of Hippuric Acid in Urine, J. Biol. Chem. **11**:257, 1912.

times as high as normal. However, it is likely that phenylpyruvic acid reduces the Folin-Denis reagent; therefore no definite conclusion can be drawn as to whether phenolic derivatives show definite increase.

*Results and Comment.*—The essential biochemical feature of the disease is the presence in the urine of phenylpyruvic acid, which was isolated and identified. From benzene it crystallizes in fine needles; its melting point is from 155 to 157 C. It is almost insoluble in cold water, benzene and chloroform and is readily soluble in alcohol and ether.

A quantitative determination of the daily output of phenylpyruvic acid was obtained in 8 patients. The figures varied from 0.68 to 2.8 Gm., the diet being mixed. Repeated determinations in the same patient yielded practically constant figures, the diet being the same.

One patient was given by mouth 5 Gm. of pure sodium phenylpyruvate, corresponding to 4 Gm. of the acid. The diet had been free from proteins for five days. The daily urinary output of the compound, which had been for several days about 0.6 Gm., increased to 2.2 Gm. on the day of the experiment and to 1.4 Gm. on the following day. This experiment seems to prove the failure of the patients to deal with phenylpyruvic acid in the ordinary way, since in a normal person the same amount of sodium salt is completely destroyed.

That the excreted phenylpyruvic acid is partly of exogenous origin is unquestionably proved by an increase in the urinary output of the compound after a high protein diet. This increase, though widely varying from one case to another, was constant; it reached in some instances 8 Gm. in twenty-four hours, after five days of diet.

Theoretically, it is from the aromatic portions of the protein that phenylpyruvic acid derives, since there is no evidence that synthesis of the benzene ring ever occurs in the animal body; as a matter of fact, the increase in urinary output is more marked when the protein intake contains a large percentage of aromatic fractions (such as casein or maize).

However, aromatic amino-acids (phenylalanine and tyrosine) could never be recovered from the urines with Dakin's extraction procedure,[23] not even after experimental feeding of the first two compounds. Although new experiments with higher doses are required, this result seems to indicate that the patients are able to accomplish normally the first step of the catabolism of aromatic amino-acids, i. e., deamination.

Of the three amino-acids of the protein with a benzene ring in their molecule, tryptophan was not used for feeding experiments; conversion into phenylpyruvic acid is not to be expected theoretically, since in tryptophan the benzene ring forms part of a more complex, heterocyclic group. In 1 case 10 Gm. of tyrosine was given, the patient being given a protein-free diet; the output of phenylpyruvic acid was not increased. Feeding experiments with phenylalanine were performed also in 1 case; after ingestion of 10 Gm. of *d-l*-phenylalanine an increase of from 0.8 to 2.75 Gm. in the daily urinary output of phenylpyruvic acid was observed, the patient being fed carbohydrates only. The anomaly therefore appears to be limited to the metabolism of phenylalanine. Experiments with various catabolites of aromatic amino-acids are under way.

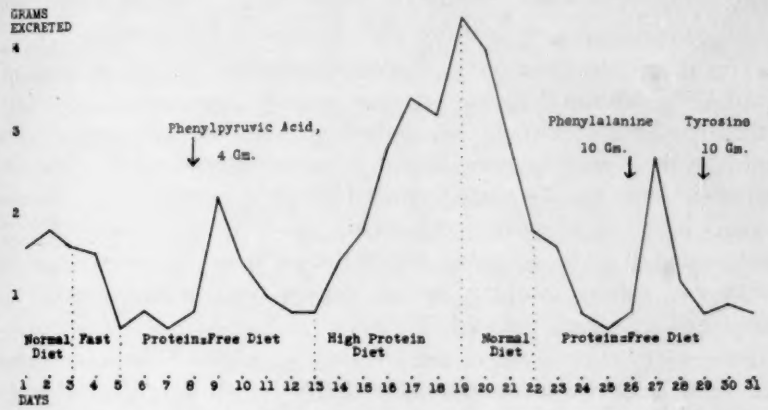
23. Dakin, H. D.: On Amino-Acids, Biochem. J. **12**:290, 1918.

Both after fasting for forty-eight hours and with a diet free from protein, a certain amount of phenylpyruvic acid, varying from 0.28 to 0.8 Gm. daily, was still excreted by 3 patients, an amount which it seems reasonable to consider of endogenous origin. The proteins of the tissues, therefore, appear to be implicated in this error of metabolism.

However, in a fourth patient phenylpyruvic acid disappeared from the urine after forty-eight hours' fasting, following seven days of protein-free diet.

Graph 2 shows the output of phenylpyruvic acid in a patient under various experimental conditions and sums up the most significant results of the metabolic studies.

The amount of output of phenylpyruvic acid differed considerably from one case to another, both during a fast and with a given diet. Moreover, the increase of excretion following ingestion of the same amount of casein varied from one patient to another. Therefore, although more conclusive evidence is needed, it seems justifiable to assume that the failure to deal with phenylpyruvic




Graph 2.—Urinary output of phenylpyruvic acid in various feeding experiments.

acid may be of various degrees—from partial to almost complete inability to dispose of the compound. Whether this variability in dealing with the acid is in some relation to the degree of the mental defect remains unascertained, although in some of the patients of lowest grade the highest figures in output were obtained.

The data so far obtained do not rule out the presence of other hypothetic catabolites of phenylalanine (phenyl-lactic, phenylacetic and phenylaceturic acids). These, if present, were quantitatively titrated with phenylpyruvic acid, the final product of oxidation being the same in the procedure of determination already described. However, attempts to recover these abnormal compounds have failed so far. The discussion has been limited, therefore, to phenylpyruvic acid.

From these preliminary experiments it appears that phenylalanine is the main, if not the only, source of the phenylpyruvic acid excreted in the urine of the patient. It is, indeed, a classic contention that phenylpyruvic acid is a necessary step in the metabolism of phenylalanine, resulting from a primary oxidative deamination of the latter prior to

disruption of the benzene ring (Dakin [24] and Neubauer [25]). New evidence for this assumption has been produced recently both in feeding experiments in rabbits (Shambaugh and others [26] and Chandler and Lewis [20]) and in perfusion experiments in surviving tissues (Krebs [27]). However, it has been maintained by other investigators that the path of oxidation of phenylalanine passes through tyrosine, breaking down along the lines of parahydroxylphenylpyruvic acid. This second theory is based on experiments of Embden and Baldes,[28] who failed to find aceto-acetic acid following perfusion of phenylalanine in the surviving liver, whereas they isolated traces of tyrosine. These results, which were questioned by Dakin [24] have been confirmed recently by Edson.[29] The observation of Medes [30] in a case of tyrosinosis that the urinary output of Millon-reacting substances increased after ingestion of phenylalanine is new evidence for the hypothesis of a nuclear hydroxylation of phenylalanine, with formation of tyrosine derivatives.

This theoretical question is of much importance for the understanding of the biochemical nature of phenylpyruvic oligophrenia. In fact, if the hypothesis of a common metabolic path for tyrosine and phenylalanine is true, phenylpyruvic acid may be considered not as a normal catabolite but as an abnormal product formed by perverted metabolism of phenylalanine; whereas if the classic theory is maintained, phenylpyruvic acid may be regarded merely as an intermediate product of normal metabolism, escaping further changes in the organism of the patient and therefore excreted as such.

From a critical analysis of the literature, already briefly referred to, there is sufficient evidence to assume that although the transformation of phenylalanine to tyrosine may be an alternative path in the catabolism of the former, the preferential path runs through phenylpyruvic acid.

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24. Dakin, H. D.: Oxidation and Reductions in the Animal Body, ed. 2, London, Longmans, Green & Co., 1922.

25. Neubauer, O.: Intermediärer Eiweiss-stoffwechsel, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1928.

26. Shambaugh, N.; Lewis, H., and Tourtellotte, D.: Comparative Studies of the Metabolism of the Amino-Acids: Phenylalanine and Tyrosine, J. Biol. Chem. **92**:499, 1931.

27. Krebs, H.: Untersuchungen über den Stoffwechsel der Aminosäuren im Tierkörper, Ztschr. f. physiol. Chem. **217**:191, 1933.

28. Embden, G., and Baldes, K.: Ueber den Abbau des Phenylalanins im tierischen Organismus, Biochem. Ztschr. **55**:301, 1913.

29. Edson, N. L.: Ketogenesis-Antiketogenesis: Ketogenesis from Amino-Acids, Biochem. J. **29**:2498, 1935.

30. Medes, G.: A New Error of Tyrosine Metabolism: Tyrosinosis, Biochem. J. **26**:917, 1932.

The biochemical nature of phenylpyruvic oligophrenia, therefore, appears to consist of stoppage of the metabolism of phenylalanine at the first stage, i. e., alphaketonic acid. In its biochemical significance of the failure of oxidation of aromatic amino-acids, the disease may thus be regarded as similar to alkaptonuria and tyrosinosis, both of which involve a block in the oxidation of tyrosine, at different stages.

There is excellent ground to assume that the oxidation of a single product of metabolism may be impaired without affecting the capacity of the body to oxidize other substances (Dakin [24]), since it appears likely that oxidizing agents bear a special relation to the substance undergoing change. Such a specificity seems to exist for the catalysts involved in the oxidation of phenylalanine (Bernheim and Bernheim [31]). As Garrod suggested for other inborn errors of metabolism, the mechanism of the biochemical anomaly may be traced, therefore, to a congenital lack of some particular enzyme which normally brings about the transformation of phenylpyruvic acid.

However, this tentative explanation of the biochemical nature of phenylpyruvic oligophrenia as an inborn failure to oxidize further an intermediate product of metabolism leaves open the fundamental question of the significance of the association of the metabolic error with the clinical picture. It is, indeed, well known that the inborn metabolic errors known so far occur without any clinical syndrome or clinical signs and are secondary and not necessary manifestations of the chemical error (e. g., urinary calculi in cystinuria and ochronosis in alkaptonuria), whereas in phenylpyruvic oligophrenia severe involvement of the nervous system, manifesting itself in both mental defect and a variety of neurologic signs, always coexists with the metabolic anomaly.

At first sight, one is tempted to regard the presence of phenylpyruvic acid as an anomaly, biochemical in character, to be compared with and having the same significance as morphologic anomalies which are frequent in mentally defective persons.

As Garrod [32] pointed out, a malformation by defect appears to be due to arrest of the process of development, so that some portion of the body is left unfinished; likewise, an inborn error of metabolism results from failure of some step in the series of chemical changes which constitute metabolism, being most nearly analogous to a malformation by defect.

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31. Bernheim, F., and Bernheim, M.: The Oxidation of Tyrosine and Phenylalanine by the Livers and Kidneys of Certain Animals, J. Biol. Chem. **107**:275, 1934.

32. Garrod, A. E.: Inborn Error of Metabolism, ed. 2, London, Oxford University Press, 1923.

In this respect phenylpyruvic oligophrenia appears to be a unique instance of developmental deficiency, biochemical in character, in the vast group of deficiencies of development which constitute the essence of primary mental deficiency.

However, the analogy between morphologic and biochemical anomalies ought not be carried to the misleading assumption that the presence of phenylpyruvic acid is an accidental feature casually coexisting with mental deficiency, like harelip, cleft palate or spina bifida. Such a simple analogy encounters serious difficulties: First, the metabolic error, even if frequently associated with mental deficiency, should be found also in mentally normal persons; so far this has never been observed. Second, excretion of phenylpyruvic acid should occur in various and different forms of mental deficiency, whereas it actually coexists with a definite form, with physical and mental characteristics of its own. Therefore, from a clinical point of view it appears justifiable to regard the metabolic error, the mental deficiency and the neurologic syndrome as the essential constituents of a morbid unity.

Finally the question may be raised from a pathogenic point of view whether the primary lesion is to be seen in the biochemical changes or in the alterations in the nervous system. That the involvement of the nervous system is secondary to and determined by the metabolic error seems to be unlikely. Experiments on kittens were performed in order to test the toxicity of the phenylpyruvic acid and its effects on growth and development; the results so far have been without significance, showing no difference in growth between animals which were given injections and those used as controls. Moreover, toxic symptoms were not observed with daily doses of 0.25 Gm. On the other hand, in the absence of a pathologic control (in no case was autopsy performed), there is no ground for inferring that some specific lesion of the nervous system is responsible for the metabolic anomaly. Therefore, although the greatest caution is necessary in drawing conclusions, it appears likely that both the involvement of the nervous system and the metabolic error are the expression of the same degenerative process, genetic in character.

## SUMMARY

1. A preliminary study of 50 cases of mental deficiency associated with excretion in the urine of phenylpyruvic acid is presented.

2. Critical examination of the anamnestic data seems to exclude any relation of exogenous agencies to the etiology of the disease, whereas the family incidence of the disease suggests that a genetic mechanism is of etiologic significance.

Statistical elaboration and critical analysis of the genetic figures afford justification for regarding the condition as determined by a single recessive gene substitution.

3. Clinically, the disease appears to constitute a fairly well defined syndrome, characterized by pronounced intellectual defect coexisting with neurologic symptoms. These consist of extrapyramidal manifestations (rigid posture, muscular hypertonus and hyperkinesias) and exaggeration of the deep reflexes. Moreover, characteristic constitutional features are found in the majority of cases.

4. From a biochemical point of view the condition appears to be an error of the metabolism of phenylalanine, consisting essentially of a failure to oxidize further a normal catabolite, phenylpyruvic acid, which consequently is excreted as such in the urine.

# "COLD PRESSOR TEST" IN TENSION AND ANXIETY

## A CARDIOCHRONOGRAPHIC STUDY

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### REVIEW OF THE LITERATURE

*Heart Rate-Tachycardia and Anxiety.*—The increased pulse rate in anxiety states is so well recognized that some psychiatrists question the existence of true anxiety in its absence. In the full-blown acute anxiety state palpitation as a symptom of tachycardia and other factors is all but universal. The clinical picture in such an attack corresponds in many respects to that produced by the normal changes associated with excessive exertion and represents a physiologic symptom complex. In persons suffering from the debilitation of such diseases as influenza, typhoid, tuberculosis or hyperthyroidism, the threshold to the precipitation of this symptom complex is reduced, and it may appear in a state of normal or even diminished physical exertion. Da Costa [1] studied the appearance of this syndrome in the soldiers engaged in the Civil War in this country. Lewis,[2] during the World War, made an exhaustive study of soldiers returned to base hospitals supposedly suffering from heart disease. These men had been separated roughly into two groups—those suffering from valvular disease of the heart and those suffering from disordered action of the heart. Lewis found that practically all the men in the group with disordered cardiac action and a large number of those in the group with valvular disease were suffering from exaggerated symptoms of physical exertion. He discussed the rôle of fear in the production of these symptoms and studied the debilitating factors which seemed to predispose to their development.

In addition to these acute circulatory symptoms of anxiety, there are a multitude of other manifestations of disturbance of the auto-

From the Department of Psychiatry, the Yale University School of Medicine.

1. Da Costa, J. M.: On Irritable Heart, Am. J. M. Sc. **61**:17-52, 1871.

2. Lewis, T.: The Soldier's Heart and the Effort Syndrome, New York, Paul B. Hoeber, 1918.

nomic nervous system—sweating, hyperpnea, goose flesh, dryness of the mouth, flattening of the gradient of the upper gastro-intestinal tract [3] and in some instances irritability and spasm of the colon.[4] These physiologic components of anxiety are present in many mental and emotional disorders in which chronic insecurity and anxiety exist, even in the absence of acute panic states. In some clinics these subacute manifestations are referred to as tensional. As tension may exist in the absence of anxiety and differentiation between patients suffering from these subacute symptoms and persons suffering from acute panic states seems to be quantitative rather than qualitative, the term anxiety is used in this paper to refer to the entire group.

The syndrome of the overactive heart observed in anxiety states corresponds physiologically with the effort syndrome and clinically with neurocirculatory asthenia. Harrison [5] labeled it the "hyperkinetic syndrome," by which he implied that the heart is overactive not only in rate but in minute-volume output. He contrasted this syndrome with that in secondary surgical shock or during the period of collapse following extensive burns, in which the venous return to the heart is inadequate and the increase in ventricular rate is accompanied by a decrease in stroke volume. In their classic forms clinical differentiation between these two pictures of tachycardia is clear, but in less severe or in complicated forms it is difficult. This differentiation, however, may be significant in the study of emotional disorders.

Henderson, Haggard and Dolley [6] stated that in the normal person the stroke volume of the heart remains constant and that the circulation, therefore, is proportional to the cardiac rate. There are two exceptions to this—the heart of the trained athlete, which, they stated, increases in stroke volume as the rate becomes elevated, and that of the tobacco smoker, in which, they said, elevation of the rate is accompanied by a decrease in stroke volume. The conclusions of Henderson, Haggard and Dolley were based on a study of respiratory exchange. Studies of cardiac output were not made. Their work would tend to place the tobacco smoker's heart in the class of Harrison's hypokinetic syndrome and to ally its action with that of the heart in

3. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear, and Rage, ed. 2, New York, D. Appleton & Co., 1929, pp. 12-16. Alvarez, W. C.: The Mechanics of the Digestive Tract, New York, Paul B. Hoeber, Inc., 1928.

4. Jordan, S. M., and Kiefer, E. D.: The Irritable Colon, J. A. M. A. **93**: 592-595, (Aug. 24) 1929.

5. Harrison, T. R.: Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1935, pp. 31-36.

6. Henderson, Y.; Haggard, H. W., and Dolley, F. S.: The Efficiency of the Heart, and the Significance of Rapid and Slow Pulse Rates, Am. J. Physiol. **82**:512-524, 1927.

secondary surgical shock, thus placing the palpitation which follows smoking and that of the effort syndrome in separate categories.

Particular emphasis has been placed on patients who complained of physical symptoms which appear to have resulted from endocrine and efferent neurogenic stimuli associated with underlying anxiety, and the patients have been grouped arbitrarily on this basis.

The purpose of this report is to describe the effects of standardized emotionally disturbing situations (cold pressor test) on the variability in rate of the individual heart beats and on that of the average heart rate in patients presenting symptoms of anxiety.

## MATERIAL AND METHODS

The material for this study was selected primarily from the psychiatric wards of the New Haven Hospital. In the diagnostic summaries the terms anxious and hysterical have been employed in the wide sense. For example, all manifestations arising from the autonomic nervous system characteristic of the state produced by fear were considered to have their origin in anxiety, whether they occurred in psychically normal persons under external stress, or in psychopathic persons whose milieu in itself was insufficient to produce the state. In a study of the patients an effort was made to picture the degree of subjective fear in each instance, but inclusion in one or another of the subgroups of patients with anxiety depended on the physical components. In most cases there were circulatory symptoms. Spastic constipation, however, was considered an adequate indication for inclusion in the anxious group, and in two instances patients were included in this group on the basis of gastro-intestinal symptoms in the absence of palpitation or dyspnea. The term hysterical was employed to describe purposeful symptoms suggestibly determined, as well as those frankly dissociative and dysmnesic.

For the purposes of a general survey of data the subjects were divided into six groups.

GROUP A.—*Normal subjects as controls.*

This group of fourteen persons was recruited largely from physicians, nurses and employees in the hospital and was essentially unselected, except for the omission of one person with frank symptoms of disorder of the autonomic nervous system.

GROUP B.—*Nonpsychotic patients with somatic and subjective evidences of tension and anxiety.*

This group of eleven persons, with one exception, represented patients who had sufficient symptoms to justify admission to the hospital wards. The presenting symptoms were of an anxious and tensional nature. Some patients had had frank, acute, circumscribed "anxiety attacks." Others were disabled with more chronic manifestations, which in two instances were primarily those of disturbance of the gastro-intestinal tract. On physical examination all these persons showed stigmas of imbalance of the autonomic nervous system.

GROUP C.—*Psychotic patients presenting no symptoms of tension or anxiety.*

This group consisted principally of schizophrenic and manic-depressive patients. There were two with organic lesions. The total number of the group was nine.

GROUP D.—*Psychotic patients with subjective and somatic evidences of anxiety.*

This group of five persons consisted primarily of patients with tensional manifestations of depression. One schizophrenic patient was included.

GROUP E.—*Patients with hypertension.*

There were five patients in this group. An attempt was made to determine the degree of anxiety present in these patients. Two showed no subjective or somatic evidence. One was extremely anxious and tense. Because of language difficulties, it was difficult to make an accurate estimate for the other two, but both were hypochondriac, irritable and excitable and showed some evidence of fear.

GROUP F.—*Psychopathic persons with various unrelated disorders.*

Six of these patients were primarily hysterical or hypochondriac, which rendered an evaluation of the somatic symptoms practically impossible. One patient was suffering from a chronically and seriously hampered energy output, which would have earned for him the label "neurasthenia" if that term had been used. There were seven patients in the group.

## APPARATUS

For continuous recording of the heart rate the cardiochronograph was employed. This apparatus is the outgrowth of the cardiotachometer of Boas[7] and his co-workers. The instrument consists of a vacuum tube amplifier which magnifies the action current of the heart taken from electrodes on the chest to a point at which it will trip a relay. The pulse beats are then recorded with a cyclometer, from which the total number of beats for any given time and the average rates may easily be computed. Studies were made by Boas and Goldschmidt[8] on the subjects who wore the apparatus for many hours at a time; they demonstrated diurnal variations in the pulse rate during relatively normal activity. A satisfactory recording device, which would show the minuter variations in the heart rate, was never developed.

Boas' amplifier was manufactured by the General Radio Corporation of Cambridge, Mass., and a similar amplifier furnished by them formed a part of the instrument used in this study. The recording device was developed by Bennett and Brown, of New Haven, Conn. It depends on the principle of friction and recoil and records the intervals between the individaul pulse beats as ordinates on waxed kymograph paper, which is drawn at a constant speed across a horizontal roller. A weight, attached to the stylus by a small rubber cord run over a pulley, tends to retract it to the base line. A long narrow band of steel attached to the other side of the writing point lies in frictional contact with a constantly revolving drum, a point on the circumference of which moves at the rate of 4 inches (10 cm.) per second. During the intervals between the heart beats the strip of metal is held firmly against the revolving drum by a strong electromagnet, which exerts its force at considerable mechanical advantage on a roller at the proximal end of a lever. Thus, during the intervals between the beats the metal strip and the stylus move away from the base line, at the rate of 4 inches (10 cm.) per second. At the time of each heart beat, however, the amplified action current trips a relay, which in turn breaks for one-fifth second the circuit supplying the electromagnet. During this one-fifth second a spring pulls the lever so as to relieve the pressure of the roller against the strip of metal and to obviate the friction between the metal and the drum. In this interval of recoil the stylus is pulled by the elasticity of the

7. Boas, E. P.: The Cardiotachometer, Arch. Int. Med. **41**:403-414 (March) 1928.

8. Boas, E. P., and Goldschmidt, E. F.: The Heart Rate, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

cord and the force of gravity back to the base line. Thus, after each heart beat the stylus returns to the base line for one-fifth second. It then starts moving away from it at the rate of 4 inches (10 cm.) per second until the next beat comes through. The heights of the ordinates on the graph (fig. 1) vary inversely with the rate of the heart. Two electrodes of German silver manufactured by the Sanborn Company, of Cambridge, Mass., were used to connect the subject with the amplifier.

A recording device, also employing the principle of friction and recoil and recording the intervals between the individual pulse beats as ordinates, was developed in Europe by Fleisch.[9] This apparatus differs from the one we employed in that the point of friction and recoil occurs between the revolving drum and the shaft on which it turns rather than between a piece of sheet metal and the surface of the drum. The stylus is attached permanently to the drum with a fine cord, and the drum is allowed to spin freely during the period of recoil. Fleisch's recorder

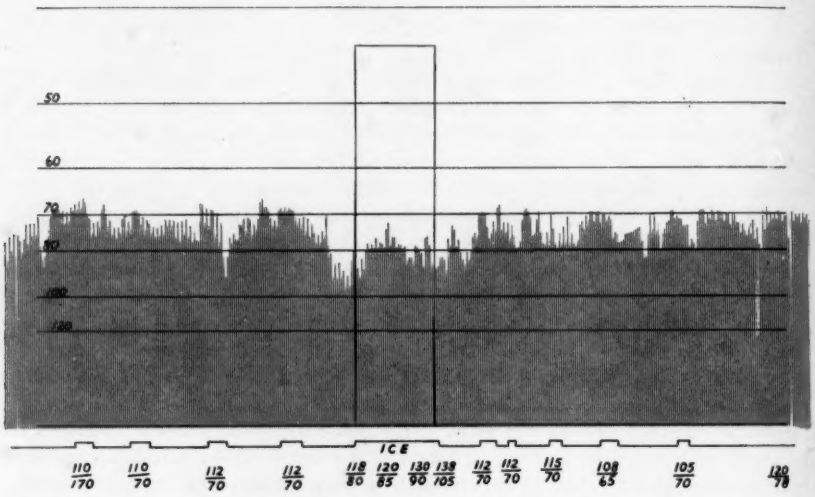


Fig. 1.—Cardiochronographic record of one of the normal subjects who was free from symptoms of tension and anxiety. The heights of the vertical lines are in inverse relationship to the heart rate. The figures along the ordinate represent beats per minute. The elevations made by the marker indicate the periods at which determinations of blood pressure were made and the one minute of stimulation with ice. Note that the heart rate increased little during the period of stimulation with ice.

is activated not by the amplified action current of the heart but by a mercury contact dependent on a plethysmograph which picks up the patient's radial pulse.

Whitehorn, Kaufman and Thomas[10] modified Fleisch's recording device and coupled it with an amplifier of the type manufactured by the General Radio Cor-

9. Fleisch, A.: Der Pulszeitschreiber, Ztschr. f. d. ges. exper. Med. **72**:384-400, 1930.

10. Whitehorn, J. C.; Kaufman, M. R., and Thomas, J. M.: Heart Rate in Relation to Emotional Disturbances, Arch. Neurol. & Psychiat. **33**:712-731 (April) 1935.

poration. They introduced the term "cardiochronograph," which adequately describes the function of the instrument. The principle of the apparatus used here is sufficiently similar to that of their instrument to suggest the adoption of their term in the interest of uniformity in nomenclature.

The use of the vacuum tube amplifier, which was introduced by workers in this country, presents theoretical as well as practical advantages over the plethysmographic contact employed by Fleisch. The increment and decrement of the peripheral pulse may vary considerably, and with such a device contact may be made at various points in the cardiac cycle. By employing the action current of the heart, however, there is reasonable assurance that the recorded beat occurs at a relatively uniform point within the QRS-T interval, a sufficiently short period in the cardiac cycle to insure accurate and constant recording. The simple electrodes on the chest give freedom of movement for the subject and do not require the active cooperation of the patient in the experiments, as do other mechanical devices for recording pulse or heart rate. Intensive study of cardiochronographic records depends on an accurate method of reading the potential rates of the individual beats. From the information that during the pulse intervals the stylus moves at the rate of 4 inches (10 cm.) per second and does so constantly except during one-fifth second interval of recoil, an equation for the calculation of the ordinate representing any given pulse rate may be easily derived:

Let x = length of ordinate
Let y = rate in terms of beats per minute
4 inches = distance stylus moves per second
4 inches × 60 = 240 = potential distance stylus could travel in one minute
$\frac{240}{y}$ = distance stylus travels per beat without allowance for one-fifth second interval of recoil
4 inches × ⅕ = 0.8 inches, potential distance per beat lost, owing to interval of recoil

$$x = \frac{240 \text{ inches}}{y} - 0.8 \text{ inch}$$

From this equation a graph was prepared and transposed to a transparent celluloid triangle. For reading, the records were placed on a drawing board, and a long T square was laid along the base line and secured there with two small C clamps. With this arrangement it was necessary only to superimpose the graduated transparent celluloid triangle in order to read off from the scale the interval between any two successive beats in terms of beats per minute.

## EXPERIMENTAL PROCEDURE

In order to obtain comparable records for different persons, the pulse rates were studied during rest and after various kinds of stimulation. The difficulty in finding an emotional stimulus of equal value to all patients led to the use in this study of a physiologic stimulus, the immersion of the hand in ice-water for one minute. This stimulus was suggested by the work of Hines and Brown.[11] Although Allbutt[12] reported in 1915 on the effect of stimulation with ice on the blood pressure, his data were apparently obtained by the local application of solid ice to the brachium, a method of stimulation which had been introduced into the study of hypertension and arteriosclerosis by Romberg[13] as early as 1904.

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11. Hines, E. A., and Brown, G. E.: The Cold Pressor Test for Measuring the Reactibility of the Blood Pressure, Am. Heart J. **11**:1-9, 1936.

12. Allbutt, C.: Diseases of the Arteries, Including Angina Pectoris, London, Macmillan & Co., 1915, p. 162.

13. Romberg, E.: Ueber Arteriosklerose, Verhandl. d. Kong. f. inn. Med. **21**: 60-94, 1904.

The mere adjustment of the bowl of ice beside the patient, with its attendant ritual, served as an emotional stimulus to the majority of patients, and although there was some differential value in its effect on different persons, it nevertheless contributed definite information, and this period was studied in every case.

Sample periods were observed at rest, during the minimal emotional stimulus of adjusting the bowl of ice and, finally, during the time when the hand was actually immersed in ice-water. It was found that moving the hand from the side of the couch and dropping it into the bowl of ice was an insufficient stimulus to produce an appreciable change in the pulse rate. In some instances, notably in hypertensive patients, the ice-water was found to produce such acute distress as to limit the period of immersion to somewhat less than one minute.

In addition to determinations of the pulse rate, the procedure of the cold pressor test of Hines and Brown was carried out in detail. After the initial resting period and the adjustment of the ice bowl beside the patient, a series of blood pressure readings was taken. After a fairly constant level was obtained, the patient's hand was immersed in ice-water, and as many readings as possible were taken during that minute. After removal of the hand from the stimulus the pressure was taken at thirty second intervals for two minutes and subsequently at one minute intervals until the resting level was again attained. In grouping the patients on the basis of their pressor responses, the lowest reading during the resting period, the highest during stimulation with ice-water and the reading two minutes after removal of the hand from ice-water were tabulated. The patients were divided into "normal," "normal hyperreactive" and "hypertensive" groups, on the basis of the criteria established by Hines and Brown. Classified as normal were persons whose blood pressure showed an increase of less than 22 mm. of mercury in the systolic or the diastolic level and whose actual readings during stimulation did not exceed 145 mm. of mercury in systolic or 95 mm. of mercury in diastolic pressure. In the normal hyperreactive group were placed all persons with normal blood pressure levels on routine examination who showed an increase in systolic or diastolic pressure of more than 22 mm. of mercury or whose systolic or diastolic pressure during stimulation exceeded 145 or 95 mm. of mercury, respectively. In the hypertensive group were placed all persons whose blood pressure on routine examination exceeded 145 mm. of mercury in systole or 95 mm. of mercury in diastole.

The procedure used as a routine consisted in placing the electrodes of the cardiochronograph on the subject and allowing him to lie on a couch for a sufficiently long time to establish resting pulse and blood pressure levels. In most instances the studies were made at least two hours after meals and after the patient had been reclining for at least one-half hour. The ice-water was placed beside the patient; a blood pressure cuff was fitted on his left arm and a series of basal blood pressure readings taken. The right hand was then immersed in ice-water for one minute and was subsequently returned to the couch, where the patient was allowed to remain quietly at rest. The heart rate was recorded throughout the period.

For comparison with the heart rates recorded by the cardiochronograph, the highest and the lowest radial pulse observations during the patient's stay in the ward were secured, and for comparison with the blood pressure readings, those made at the initial physical examination were also obtained.

### METHOD OF GRAPHIC REPRESENTATION

In order to describe adequately the cardiochronographic record, it proved desirable to find some way in which to express graphically not only the average rates over sample periods but the beat to beat variability of the heart rate.

Figures 1, 2 and 9 show how variable the individual pulse beats may be and how they fail entirely to conform to the rhythm of the respiratory cycle. Mackenzie,[14] in fact, pointed out that true sinus arrhythmia is rare in adult life but that fluctuating irregularities occur independently of respiration. It was found lucid, if somewhat laborious, to express this beat to beat variability in terms of the standard deviation from the mean. The method of calculating the standard deviation is adequately described in textbooks on statistics.[15] Roughly, 68 per cent of the determinations fall within the standard deviation.

The average rates were taken from the mathematical means of the measured individual beats and were compared with the number of observations per minute.

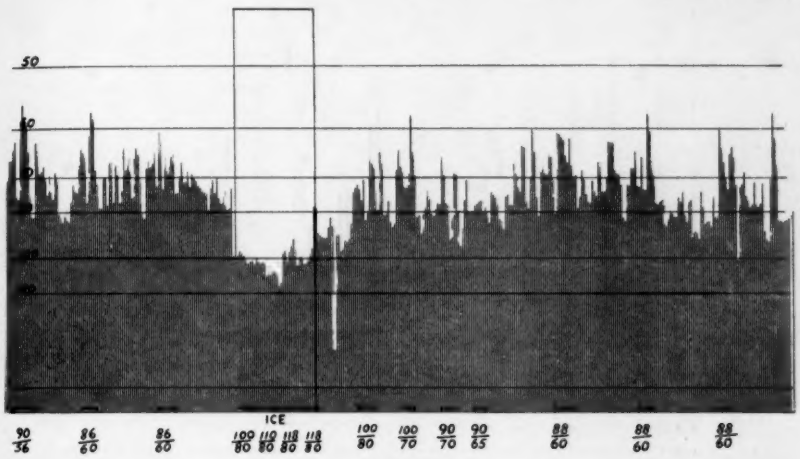


Fig. 2.—Cardiochronographic record of a patient with symptoms of anxiety. See figure 1 for explanation. Note the irregularity in the height of the lines and the marked shortening of the lines, which indicates an increase in the heart rate, during the period of stimulation with ice-water.

In this way the accuracy of the cardiochronograph was checked. Jellinek and Fertig[16] developed a planimetric method of obtaining average rates over short periods of observation, but as the individual measurements were made in this case, their method did not serve to simplify the problem.

The expression of the beat to beat variability of the heart rate in terms of standard deviation required squaring and extracting the square roots of large

14. Mackenzie, J.: Diseases of the Heart, ed. 4, New York, Oxford University Press, 1925, pp. 117-124.

15. Fisher, R. A.: Statistical Methods for Research Workers, ed. 4, Edinburgh, Oliver & Boyd, 1932.

16. Jellinek, E. M., and Fertig, J. W.: A Method for the Estimation of Average Heart Rates from Cardiochronographic Records, J. Psychol. **1**:193-199, 1936.

numbers of figures, a task which was made possible by the cooperation of the department of statistics.[17] A simpler and perhaps equally suitable method of representing similar variations is to calculate percentiles, which are merely mathematical averages of a specified number of beats at the two extremes of the scale.

The samples of the cardiochronographic record were selected for study as follows: During the resting period and after the establishment of a relatively constant heart rate, several short samples totaling one minute were selected. In some instances, when the paper on the kymograph drum had been moving at the rate of 4 inches (10 cm.) per minute, it was possible to pick six periods of ten seconds each at random. In other instances, when the drum had been operated at the rate of 1 inch (2.5 cm.) per minute, it was impracticable to select more than two periods of thirty seconds each. From the period of minimal emotional stimulus

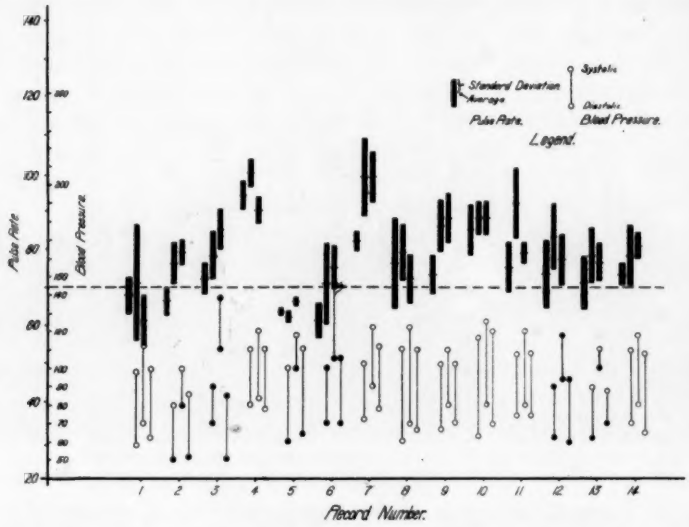


Fig. 3.—Group of normal subjects free from symptoms of tension and anxiety. The figures represent a summary of the cardiochronographic records. Each group of three bars describes one experimental period for one subject. In reading from left to right, the first bar represents the mean heart rate and the standard deviation during the period of rest, the second bar these values during minimal emotional stimulation and the third bar the values during stimulation with ice-water. The blood pressures are shown immediately below the bars. The first reading is the basal blood pressure; the second is the maximal reading during the period of stimulation with ice, while the third is the blood pressure two minutes after withdrawal of this stimulus. The solid black circles indicate a rise in blood pressure of more than 22 mm. of mercury.

a one minute example was selected in each case. Two subjects could not tolerate the discomfort of stimulation with ice-water for an entire minute, but with this exception the period of observation was uniform and of one minute's duration.

17. Mr. Frank Shuttleworth assisted in directing this work.

In the illustrations (figs. 3 to 7) the average heart rates are represented by short horizontal lines and the standard deviations by vertical bars above and below the averages. In this way each observed sample was recorded, so that the average heart rate, the standard deviation and the rise or fall in rate from a previous observation could be readily observed. Each group of transverse lines and of vertical bars represents the average heart rate and the standard deviation for one patient. The symbol to the left records the resting sample; that in the center stands for the period of minimal emotional stimulation, while that on the right indicates the period of stimulation with ice-water. Below these symbols and keyed to a different scale are circles representing blood pressure readings. The circles connected by solid lines represent, from left to right, the blood pressure

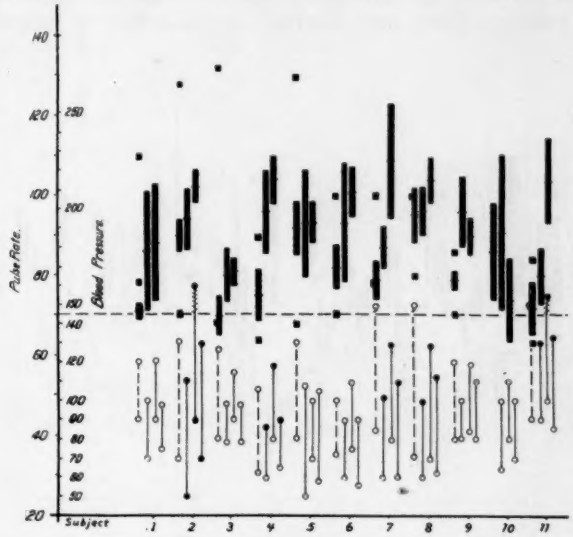


Fig. 4.—Subjects with symptoms of tension and anxiety but no evidence of psychosis. The legend is the same as that in figure 3, except that figures are included to indicate the range of blood pressure and of pulse rate during hospitalization. The former is indicated by the figures for blood pressure connected by a broken line and the latter by the solid black squares. Blood pressures exceeding 145 mm. of mercury are indicated by a cross-hatched line.

while resting, the blood pressure during stimulation with ice-water and the reading two minutes afterward. In instances in which there was an increase of more than 22 mm. of mercury in systolic or diastolic pressure, the circles representing that phase of the cardiac cycle were filled in solid. Readings above 145 mm. of mercury were distinguished by cross-hatching above the 145 mm. level of the line connecting the systolic and the diastolic symbol.

## ANALYSIS OF DATA

The records of the individual subjects in the group used as a control (group A) are shown in figure 3, while the averages for the group as a whole appear in figure 7. The average pulse rate of

these persons was 75.5 when at rest, 81.5 during the minimal emotional stimulus and 80 during the time when the hand was immersed in ice-water. The standard deviation was ± 5.24 during rest, ± 7.44 during the period of emotional stimulation and ±4.72 when the hand was immersed in the ice-water.

Only two persons stood out as presenting heart rates considerably above those of the group as a whole; both seemed particularly stolid; one was menstruating at the time of the investigation.

The pulse rates of the group of nonpsychotic persons with anxious and tensional symptoms (group B) are recorded in figure 4. In this group the average pulse rate during rest was 81; it increased to 90

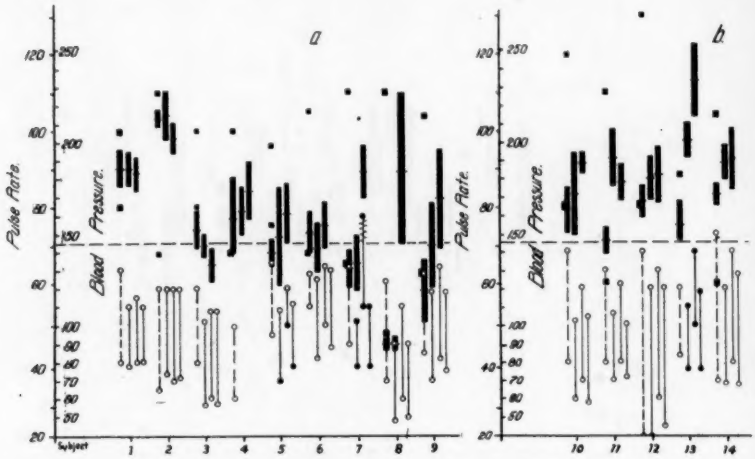


Fig. 5.—Section *a* represents psychotic patients without symptoms of tension or anxiety. The legend is the same as that in figures 3 and 4. See figure 9 and the comment for exceptional features presented by the record of subject 2. Section *b* represents psychotic patients presenting symptoms of anxiety and tension.

during the minimal emotional stimulus and to 95.5 during immersion of the hand in ice-water. During the emotional stimulus the standard deviation of the individual pulse intervals increased from the level of ± 5.6 during rest to ± 10.4, while during stimulation with ice-water it returned to ± 7.7. Thus, there was considerably greater standard deviation in this group than in the control group, and the instability became most marked during the period of the minimal emotional stimulus. The pulse rate in general was higher, and the instability greater, and during stimulation with ice-water the increase in rate was more marked.

Among the psychotic patients who presented no symptoms of anxiety (group C) was one, suspected of suffering from a neoplastic

lesion in the interpeduncular region, whose pulse rate was characterized by such marked variations that in calculating the averages for the group it seemed advisable to exclude his record. The pulse rates of the patients of the group are shown in figure 5 *a*, while the averages appear in figure 7. The corrected average pulse rate during rest was 76, that during the minimal emotional stimulus, 77 and that during stimulation with ice-water 83—figures which compare reasonably well with those for the control group. The standard deviations of the individual pulse intervals—± 5.5 during rest, ± 7.2 during the minimal emotional stimulus and ± 6.7 during the immersion of the hand in

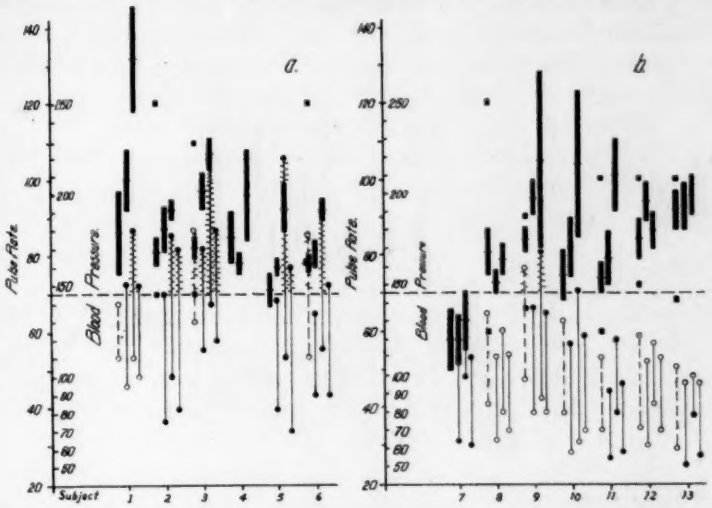


Fig. 6.—Section *a* represents patients with hypertension. The legend is the same as in figures 3 and 4. Section *b* represents psychopathic patients with various unrelated disorders.

ice-water—were again essentially the same as those for the normal group.

The psychotic patients who showed evidence of anxiety (group D) are represented in figure 5 *b*. In this group the average heart rate during rest was 78, that during the minimal emotional stimulus 90 and that during stimulation with ice 94, while the simultaneous determinations of the standard deviation were ± 4, ± 6.6 and ± 6.5. The figures for the pulse rate, thus, are closely in accord with those of the nonpsychotic anxious subjects, although the increase in standard deviation is not so large.

The records of persons of the hypertensive group (group E) are shown in figure 6 *a*. The averages appear in figure 7. The average pulse rate during rest was 79.6, that during the minimal emotional

stimulus 88, and that during stimulation with ice-water 102. During the same periods the standard deviations were ±4.77, ±5.07 and ±5.94. The increase in heart rate and the level attained during stimulation with ice-water, thus, are considerably higher than in any of the other groups, although the standard deviation is not as great as in any of the others. For one patient in this group pulse readings on two occasions were recorded.

Studies of pulse rates of the patients of the miscellaneous group (group F) are represented in figure 6 *b*. Among them the average pulse rate during rest was 78, that during the minimal emotional stimulus 82 and that during immersion of the hand in ice-water, 90.5. The standard deviations during the same periods were ± 5.47, ± 5.7 and ± 10.54. The high standard deviation during stimulation with

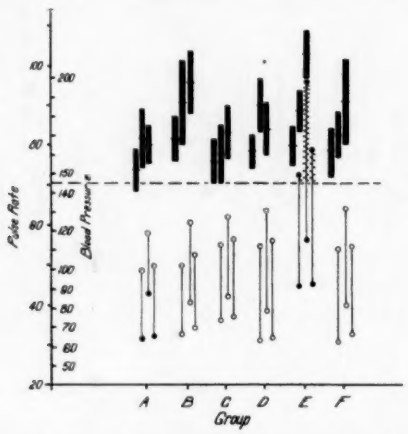


Fig. 7.—Average heart rates, standard deviations and blood pressures for the six groups recorded individually in figures 3 to 6. Each set of bars represents the average heart rate and standard deviation for one group of patients when at rest, during the minimal emotional stimulus and during stimulation with ice-water. The average blood pressures during rest, during stimulation with ice-water and two minutes subsequent to its withdrawal are indicated by the circles and connecting lines. The significance of the letters along the abscissa is as follows: *A* indicates values for controls; *B*, those for patients with symptoms of tension and anxiety but no evidence of psychosis; *C*, those for psychotic patients without evidence of anxious symptoms; *D*, those for psychotic patients with symptoms of anxiety; *E*, those for patients with hypertension, and *F*, those for patients with miscellaneous psychopathic conditions.

ice-water is due principally to the records of two persons. The first of these was characterized principally by low energy output and asthenia and the second by hypochondriac complaints, with some features of anxiety.

A comparative study of the highest and the lowest pulse rate observed in the hospital wards and the extremes noted in this investigation was made, and the observations in the wards are recorded on the graphs for each of the hospitalized groups (figs. 4 to 6). There was no accurate correlation in any of the groups, and this was particularly true of the patients of the anxious group.

The pulse levels during rest of the psychotic and nonpsychotic anxious groups (groups B and D) were distinctly higher than those of the psychotic and nonpsychotic control groups (groups A and C). The two anxious groups showed greater rises during the minimal emotional stimulus than either of the control groups, while during stimulation with ice-water they reached an average heart rate exceeded only by that of the hypertensive patients (group E), who attained an average rate during stimulation with ice-water of 103. The nonpsychotic and psychotic anxious groups (groups B and D) attained average rates of 95 and 94, respectively, while the miscellaneous group (F) reached 91 and the nonpsychotic and psychotic control groups (A and C) 79 and 83. The levels and increases of the heart rate are illustrated in figures 7 and 8.

The average standard deviation for each of the six groups is represented by the length of a bar in figure 7. The standard deviations for the six groups during rest were nearly comparable, varying from $\pm 4$ in the psychotic anxious group (D) to $\pm 5.65$ in the nonpsychotic anxious group (B). During the minimal emotional stimulus, however, there was a much greater increase in standard deviation in the nonpsychotic anxious group (B) than in any of the others, and in that group it was $\pm 10.39$. The psychotic group with anxiety (D) attained a standard deviation of $\pm 6.65$; the psychotic group without anxiety (C), $\pm 6.6$; the hypertensive group (E), $\pm 5.07$, and the miscellaneous group (F), $\pm 5.7$. The standard deviations of the six groups are represented in the central graph in figure 8.

The values for blood pressure of the subjects in each of the six groups are recorded directly under the observations on the pulse rate on the same charts (figs. 3 to 7).

The average blood pressure of the control group (A) during rest (fig. 3) was 99 systolic and 63 diastolic, which was somewhat lower than that of the population at large, the rise to 118 systolic and 102 diastolic during stimulation with ice-water representing a distinct degree of hyperreaction in diastolic pressure, while the fall to 102 systolic and 65 diastolic was an expected normal finding. Although there were no hypertensive persons in the control group, there were eight diastolic hyperreactors, of whom two were also systolic hyperreactors and one attained a systolic pressure of over 145 mm. of mercury during stimulation with ice.

The group of nonpsychotic persons suffering from manifestations of anxiety (group B) (fig. 4) showed an average blood pressure during rest of 102 systolic and 65 diastolic, which did not differ essentially from that of the control group, while the increase to 124 systolic and 82 diastolic during stimulation with ice-water was somewhat higher and placed the group as a whole in the category of systolic hyperreactors. The return to 107 systolic and 69 diastolic after two minutes was essentially within the normal range. There were five systolic hyperreactors in this group, of whom one was also a diastolic hyperreactor and two showed systolic pressures over 145 during stimulation with ice-water. These figures for blood pressure are essentially in accord with the experience of Hines and Brown.[11]

Among the psychotic persons without evidence of anxiety (group C), no blood pressure readings were obtained on one patient, and her

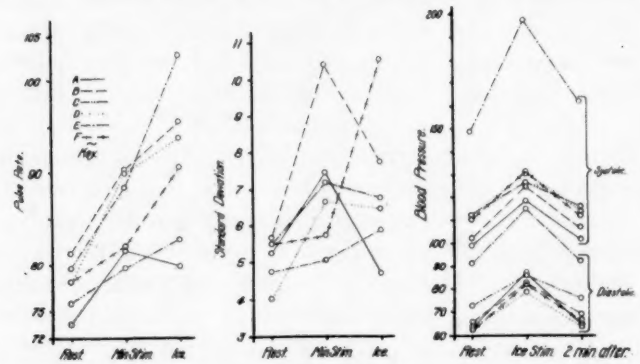


Fig. 8.—Summary of the observations on the six groups recorded in figures 3 to 6. The chart on the left represents the average of the pulse rates; that in the center, the average of the standard deviations, and that on the right, the average of the blood pressures, for each of the six groups. In designating the different groups the same letters are employed as in figure 7.

record was omitted in calculating the average for the group. The averages for the remainder of the group are recorded in figure 5 *a*. The average tension during rest, 112 systolic and 72 diastolic, rose during stimulation with ice-water to 127 systolic and 86 diastolic and was 115 systolic and 75 diastolic two minutes afterward. The group as a whole thus falls into the group of normal reactors, although individually there were two diastolic hyperreactors, one of whom showed, in addition, an increase in systolic pressure of 58 mm. of mercury and attained a systolic level of 160 mm. of mercury during stimulation.

The blood pressure readings of the group of psychotic patients with evidence of anxiety (D) are represented in figure 5 *b*. The average blood pressure level during rest of 112 systolic and 63 diastolic

rose to 130 systolic and 78 diastolic during stimulation with ice-water and fell again to 114 systolic and 64 diastolic two minutes later. The group as a whole, including the persons comprising it, falls into the class of normal reactors.

The blood pressure readings of the hypertensive group (E) are recorded in figure 6 *a*. The average blood pressure during rest was 148 systolic and 91 diastolic, that during stimulation with ice-water 197 systolic and 115 diastolic and that two minutes later 162 systolic and 92 diastolic. Of this group all were systolic hyperreactors; all reached systolic levels in the definitely hypertensive range, and all but one were diastolic hyperreactors. The findings thus confirm the observations of Hines and Brown as to the type of response seen in hypertensive patients.

The average blood pressure readings of the miscellaneous group (F) are recorded in figure 6 *b*. The average blood pressure during rest for this group was 110 systolic and 62 diastolic, that during stimulation with ice-water 131 systolic and 82 diastolic and that two minutes later 112 systolic and 67 diastolic, the group thus barely falling within the bounds of normal reactors. There were four systolic hyperreactors, for two of whom the systolic pressure reached levels over 145 and two of whom were also diastolic hyperreactors. There were two more diastolic hyperreactors, leaving only one normal reactor in the group.

Determinations of blood pressure made in the physical examination on admission are recorded for the five hospitalized groups (figs. 4 to 6). Some of these observations were made with the patients in a sitting or semirecumbent position and hence the values tend to be a little higher than those determined with the patient in the prone position. They represent a period of relatively tense emotion on the part of the patient, however, and are recorded for this comparative value to show the extent to which the ice-water stimulus approaches an emotional stimulus in its effect on the blood pressure.

## COMMENT

The most striking differences in the response of the pulse rate were observed to exist between the nonpsychotic anxious group (B) and the control group (A). The subjects suffering from manifestations of anxiety stood out in respect to their higher pulse rate during rest, their greater increase in pulse rate during the periods of minimal emotional and ice-water stimulation and their greater increase in standard deviation during minimal emotional stimulation (fig. 8 *b*).

Between the group of psychotic patients suffering from anxious and tensional symptoms and the psychotic control group the same

differences in changes in pulse rate were manifest (fig. 8*a*). The standard deviation also followed the same type of curve, becoming maximal during the period of minimal emotional stimulation, but it was not dramatically elevated, as in the nonpsychotic group. There was no essential difference between the change in pulse rate of the nonpsychotic and that of the psychotic control group, although the standard deviation for the latter group was somewhat higher during stimulation with ice-water.

Persons who are susceptible to the somatic manifestations of anxiety thus appear to have higher heart rates than normal persons, and their heart rates increase more during minimal emotional and ice-water stimulation. The increase in standard deviation during the minimal emotional stimulus, however, was found in all members of the anxious group with one exception and was apparent from the cardiochronographic records. Lewis [18] described a kind of irregularity similar to one type of beat to beat variability which we observed in our cases. He grouped it among the sinus irregularities not associated with respiration and described it as follows:

> An irregularity of the whole heart of mild degree, in which longer and shorter pauses are intermingled indiscriminately. It is not infrequent and is almost always combined with a general reduction of pulse rate . . . It is accentuated when the heart slows after it has quickened in response to exercise.

According to Lewis, all sinus irregularities are due to alterations in vagal tone. The standard deviation represents variability in the duration of the cardiac cycle, whether of the respiratory or of the non-respiratory type, but it does not differentiate them. It is much increased during the period of emotional stimulation in nonpsychotic persons who are anxious. From a mathematical point of view, one expects the standard deviation to decrease with increases in the heart rate. Although this concept is in accord with Lewis' observations, in our cases it was found not necessarily to be true.

The hypertensive group showed an even greater increase in pulse rate on stimulation than did the two anxious groups, although the initial level was lower and there was a less marked increase in standard deviation (figs. 7 and 8). This group was extremely heterogeneous, and although an attempt was made to determine the presence or absence of anxious features in the individual cases, it was almost impossible to do so. Two of the subjects were grossly illiterate. One apparently and another definitely suffered from anxious and tensional symptoms, while the other two members of the group were free from them.

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18. Lewis, T.: Clinical Disorders of the Heart Beat, ed. 6, London, Shaw & Sons, 1925.

Elaborate personality studies in early and advanced stages of hypertension have been made by Krapf,[19] who expressed the opinion that the irritability and tension observed in the early stages of hypertension are symptomatic rather than etiologic in significance. Our data do not contribute any information on this point.

There were subjects in the miscellaneous group (F) who showed marked increase in heart rate in the test but who did not admit suffering from anxiety. Among these were three persons whose heart rates were as high and as labile as those of the patients suffering from somatic manifestations of anxiety. One was characterized primarily by great fatigability, which was increased by a single glass of beer. This man's asthenia was probably, in part at least, circulatory in origin, although he never suffered from effort syndrome or from any functional gastro-intestinal disorder. He was also a timid person, who protested too vigorously of his freedom from fear. One woman suffered from suggestibly determined hypochondriac complaints having their origin in the fear of cancer. She had at one time suffered from abdominal cramps aggravated by catharsis and may have had an irritable colon, although the diagnosis could not be definitely established. Another woman came to the hospital because of obvious dissociative and dysmnesic hysterical symptoms of such severe nature as to preclude any accurate estimate of her true somatic complaints. She had, however, suffered from symptoms suggestive of a spastic colon and had had a normal appendix removed.

This miscellaneous group (F) contained persons whose condition has been particularly hard to classify accurately. It can be studied only in terms of the individual cases and affords an illustration of the complexity of the relationship between psychologic and circulatory system activities. It is probable that the patients who reacted to the tests in a manner similar to that of the anxious group were suffering from latent anxiety, which they were unable to verbalize.

An isolated observation was made in the case of one patient in the psychotic group (C) (no. 2 in figure 5 *a*). When she was resting quietly on the couch, her heart rate suddenly increased from 80 to 114 beats per minute. She was practically asleep at the time and showed no outward display of emotion. In the course of about two minutes the rate slowed to 102 and remained constant for some time. In this time she was spoken to but made no reply. The ice bowl and blood pressure cuff were adjusted, apparently without producing any emotional stimulation and with no appreciable change in pulse rate. She was assisted in placing her hand in ice-water, which she did with-

19. Krapf, E.: Die Seelenstörungen der Blutdruckkranken, Vienna, Franz Deuticke, 1935.

out complaining and without showing any evidence of discomfort. During stimulation with ice-water the pulse rate was 98. The part of her record which shows the spontaneous increase in rate is shown in figure 9. The patient was depressed and presented features strongly suggestive of schizophrenia. It was impossible to obtain the content of thought during the experiment.

From reference to the illustrations for the hospitalized groups, (B, C, D and E, figs. 4, 5 and 6), it is apparent that the extremes of the pulse observations in the wards did not correspond with those recorded during the periods of rest and stimulation. Probably the variations in the ward observations were determined by the conduct

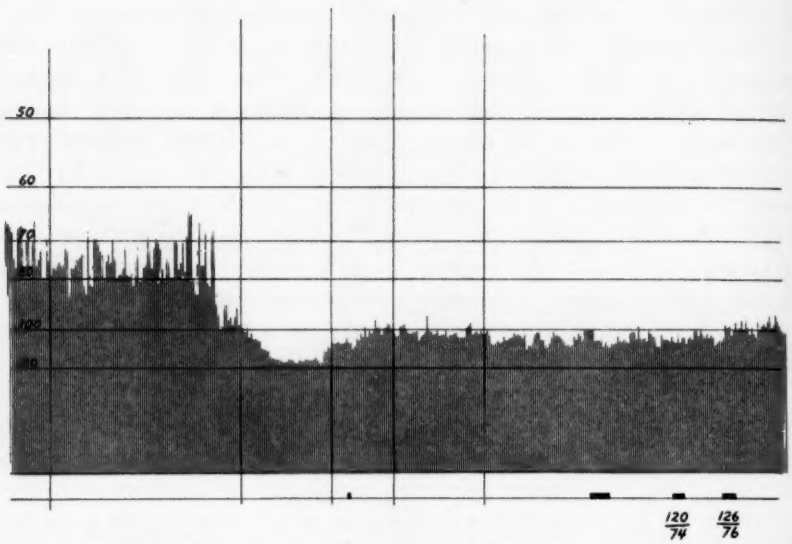


Fig. 9.—Cardiochronographic record of subject 2 of the group represented in figure 5 *a*. See figure 1 for the legend. The periods of minimal emotional stimulation and of stimulation with ice-water are represented by the two pairs of vertical lines. A spontaneous increase in rate occurred in the resting period.

of the patients rather than by the fundamental lability of their vascular systems. From reference to figure 4 it is apparent that many of the nonpsychotic anxious patients never showed particularly high pulse rates in the wards. One patient who was given to crying spells and another who was primarily an irritable, explosive person, however, had occasional high pulse rates in the ward. In the other groups, too, there was a poor degree of correlation between the extremes of the observations in the ward and those noted on the records of the cardiochronograph.

Determinations of blood pressure were made with the patient at rest and during stimulation with ice. With one exception, all the subjects showed an increase in blood pressure. Anxious persons showed a slightly greater rise than members of the control groups (fig. 8*c*). Hines and Brown, in discussing the results of the cold pressor test for measuring the reactibility of the blood pressure, said:

> The pressor responses in vasospastic disorders, Raynaud's disease, and neurocirculatory asthenia, are inclined to fall in the upper range for normal subjects. In hyperthyroidism and neurocirculatory asthenia there is an abnormal response [a rise greater than 22 mm. of mercury or to a level over 145 mm. of mercury] in the systolic pressure only.

These observations are consistent with Harrison's concept of the hyperkinetic syndrome.

The blood pressure readings for the six groups are in close accord with those which one might expect from a study of the work of Hines and Brown. The higher percentage of hyperreactors is probably to be explained on the basis of the number of basal observations made on our patients and the choice of the lowest from this group. We found that among our patients an absolutely constant basal blood pressure could not be maintained and that, particularly in the diastolic pressure, there were fluctuations. The finding of five systolic hyperreactors in the nonpsychotic anxious group is essentially in accord with the observations of Hines and Brown on neurocirculatory asthenia, while the three patients in our miscellaneous group who showed unstable and rapid heart rates also were systolic hyperreactors.

All the patients in the hypertensive group, some of whom had early arteriosclerosis, showed the classic hyperreaction described by Hines and Brown. In all instances the systolic pressure became elevated more than 22 mm. of mercury, and in all but one instance the diastolic rise also exceeded that figure.

The systolic and diastolic blood pressures for all the groups are illustrated in figure 8. Although the systolic level is no higher in the nonpsychotic anxious group than in the other nonhypertensive groups, the degree of reaction to stimulation with ice-water, 22 mm., is on the border line of abnormality. As a moderate increase in systolic blood pressure is to be expected from the increased cardiac output hypothesized in this condition, there seems to be little evidence on which to conclude that patients suffering from the effort syndrome or anxiety are potentially hypertensive.

The one patient who showed a fall in systolic blood pressure and in pulse pressure during the stimulation with ice showed no evidence of the effort syndrome but complained rather of fainting on numerous occasions. She was included in our anxious group because of her mental state, which was obviously one of anxiety, severe spastic con-

stipation and marked evidence of vasospasm on physical examination. Her hands to above the wrists and her feet to above the ankles were deeply blue, cold and moist, and their reaction to heat was suggestive of Raynaud's disease. The fall in systolic and pulse pressure suggests that the fainting was vasomotor in origin.

Study of values for blood pressure on admission in comparison with the levels obtained on stimulation with ice indicates that in many instances the fear produced by admission to the hospital has a greater pressor effect than stimulation with ice-water. This fact does not detract, however, from the value of the use of ice-water as a stimulus of relatively constant severity, nor does it detract from the value of the cold pressor test.

## CONCLUSIONS

1. A study of the pulse rate in six groups of subjects was made: (*a*) at rest, (*b*) during a minimal emotional stimulus and (*c*) during immersion of one hand in a bowl of ice-water. Determinations of blood pressure were made after the minimal emotional stimulus, during immersion of the hand in ice-water and subsequently. The subjects were grouped on the basis of subjective and somatic symptoms of tension and anxiety and on the presence or absence of psychosis. A hypertensive group and a miscellaneous group were also studied. The cardiochronograph was employed, and the intervals between the individual heart beats as well as the average heart rates were recorded.

2. The subjects who were susceptible to anxious and tensional symptoms had higher initial heart rates, and the rates increased more during stimulation than did those of the control groups. The pulse rates taken as a routine in the ward for many of these anxious patients were not remarkable. The cardiochronographic study of these persons in standard test situations provided a measure of the amount of anxiety and of its effects on the circulatory system that could not be obtained by the usual methods of psychiatric examination.

3. The irregularity of the intervals between the individual heart beats increased in all the groups during the period of minimal emotional stimulation. Among nonpsychotic patients suffering from symptoms of tension and anxiety this increase was distinctively large.

4. The hypertensive patients, even if they did not report or show anxiety, reacted to the minimal emotional stimulus with an increase in heart rate like that of the anxious patients. During stimulation with ice they reacted with a considerably greater increase in rate than the anxious patients. The increase in blood pressure was far greater than that of any other group, and at the end of two minutes, when the blood pressure of all the others had returned to the base line that of the hypertensive persons still averaged 20 mm. of mercury higher than before stimulation.

# CURVE FOR THE SUGAR CONTENT OF THE BLOOD FOLLOWING ENCEPHALOGRAPHY

## COMPARISON WITH THE USUAL CURVE FOR DEXTROSE TOLERANCE

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A study of the curve for the sugar content of the blood following encephalography was undertaken to determine whether the findings would throw light on the mechanism of regulation of the blood sugar and would be of diagnostic value in neurologic problems.

Studies of the sugar content of the blood following encephalography were made on seventy-five patients in the neurologic and neurosurgical service of Dr. Temple Fay, at the Temple University Hospital. There were twenty-eight males and forty-seven females, ranging from 10 to 62 years of age. The majority were in the 10 to 30 year age group (graph 1). These patients were grouped as follows: those with neurologic conditions, such as posttraumatic headache, spasmodic torticollis, Little's disease, postencephalitic parkinsonism and Friedreich's ataxia (fifteen); those with tumor of the brain (ten), and those with convulsive disorders (fifty).

Mader [1] in 1928 and 1932 studied the changes in the blood sugar after encephalography in thirty-two children with various neurologic conditions. He found an increase after the procedure, the sugar rising as high as 200 mg. per hundred cubic centimeters of blood in some cases. The maximum rise was on the second day, return to normal occurring in twenty-four hours. Insulin inhibited the hyperglycemia. Schönfeld [2] studied the changes in the blood sugar following the withdrawal of 15 cc. of spinal fluid in twenty-four children with neurologic conditions, such as Little's disease, epilepsy, idiocy and congenital syphilis. The blood sugar was determined immediately after spinal puncture and five, ten and fifteen minutes after the withdrawal of 15 cc. of spinal fluid. In all cases there was a rise sometimes as high as 70 points, immediately after puncture. The greatest rise (from 93 to 226 mg.) occurred in a case after encephalography. Boeters [3] reported serial determinations of the blood sugar in forty-five patients (children and adults) after encephalography.

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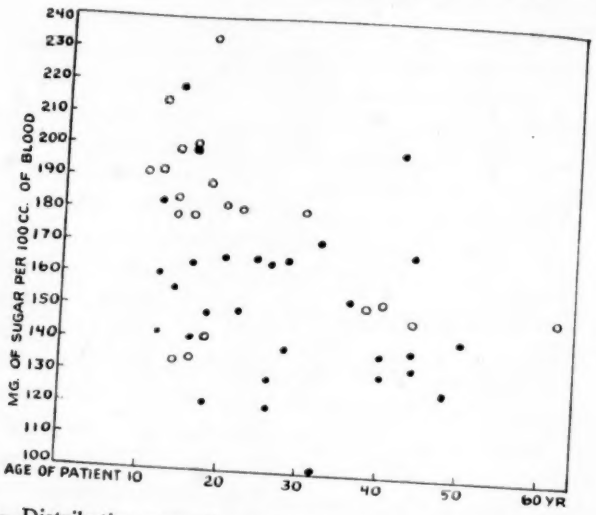
From the Department of Neurology and Neurosurgery, headed by Dr. Temple Fay, Temple University Hospital.

1. Mader, A.: Klin. Wchnschr. **11**:676-678 (April 16) 1932.
2. Schönfeld, H.: Jahrb. f. Kinderh. **138**:174-178, 1933.
3. Boeters, H.: Klin. Wchnschr. **14**:1809-1848 (Dec. 21) 1935.

He found considerable hyperglycemia, which receded until the sugar content reached a normal level after one or two hours, irrespective of the amount of air injected. He found the greatest increment (more than 100 mg.) in children. In adults he found an increase of from 40 to 80 mg. per hundred cubic centimeters of blood. Patients with cerebral tumor experienced only slight subjective discomfort. In epileptic patients with hydrocephalus he found only slight hyperglycemia.

## METHODS

The following procedure was carried out in all cases except when noted otherwise. The night before encephalography the adults were given 10 grains (648 mg.) of chloral hydrate and from 20 to 30 grains (1.30 to 1.94 Gm.) of sodium




Graph 1.—Distribution according to age and sex of the maximum values to which the blood sugar rose after encephalography. Values for patients while struggling or for those receiving a general anesthetic or atropine sulfate are omitted.

The values for males are indicated by solid circles, and those for females, by hollow circles.

bromide. On the morning of encephalography the dose was repeated, and one-half hour before injection of air 2 grains (129 mg.) of soluble phenobarbital was given hypodermically. Children received the same hypnotics in doses compatible with age. A specimen of blood for the determination of sugar was taken in each case immediately before the insertion of the spinal needles, immediately after the injection of air and at intervals of one-half, one, two, three and four hours subsequently. The specimen was then sent to the hospital laboratory for determination of the blood sugar by the Folin-Wu method.[4] The patients received no food

4. Miss M. R. Brugger, of the department of clinical pathology, headed by Prof. F. W. Konzelmann, made the determinations of the blood sugar.

during the time the specimens were taken. A few patients received 5 grains (324 mg.) of acetylsalicylic acid and chloral hydrate during this period. The average amount of air injected was about 115 cc., in cases of epilepsy, 120 cc., in cases of other neurologic conditions, and 85 cc., in cases of tumor of the brain. The first specimen of urine voided after encephalography was tested for sugar and ketone bodies.

### ADDITIONAL PROCEDURES

*A.* Two patients received ether during encephalography.

*B.* Five patients received tribromethanol in amylene hydrate during encephalography.

*C.* In ten patients a dextrose tolerance test was made from one to three days before the tests for blood sugar after encephalography. The usual dextrose tolerance test was made: A specimen of blood was taken during fasting, and the patient was then given by mouth 1.5 Gm. of dextrose per kilogram of body weight; specimens of blood were then taken in one-half, one, two and three hours, respectively, and the sugar content was estimated by the Folin-Wu method.

*D.* Thirteen patients with epilepsy received 1/100 grain (0.6 mg.) of atropine sulfate after the first specimen of blood was taken and immediately before the insertion of the spinal needles.

### EVALUATION OF VARIABLES ENCOUNTERED

*A. Hypnotics.*—According to Sollmann,[5] anesthetic doses of the barbital group and bromides and chloral hydrate in small doses cause no changes in the level of blood sugar in normal animals. Ether and tribromethanol cause temporary hyperglycemia. Cushing,[6] who minimized his own findings because of insufficient data, stated that tribromethanol causes a drop in the sugar content of the blood. Except for the few cases in which ether and tribromethanol were used,[5] the hypnotics given had little, if any, effect on the levels of the blood sugar.

*B. Struggling During Encephalography.*—The cases in which this occurred were grouped in a separate series (graph 4).

*C. Effect of Atropine Sulfate* (graph 2).—Cushing[7] found that when he injected 1 cc. of solution of posterior pituitary into the ventricles of a human brain, the patient exhibited intense flushing of the face, profuse perspiration, retching and vomiting, salivation and a marked fall in body temperature. He found that he could prevent this reaction by the subcutaneous injection of 1 mg. of atropine sulfate. It was reasoned that many of the symptoms during and after encephalography were remarkably similar to those mentioned by Cushing and were possibly also due to the liberation of posterior pituitary hormones into the cerebrospinal fluid; accordingly, 1/100 grain (0.6 mg.) of atropine sulfate was given hypodermically immediately before insertion of the spinal needles, with the intention of ameliorating these symptoms.

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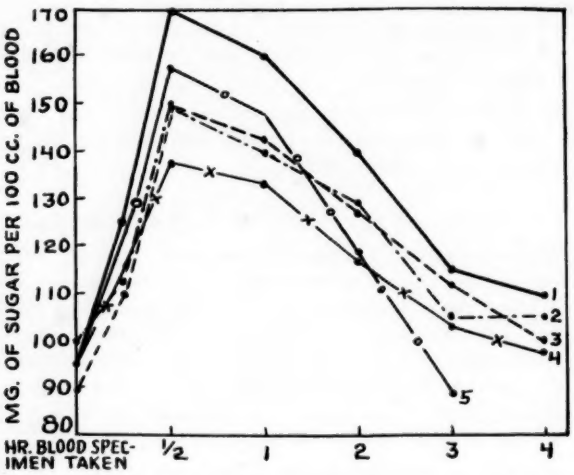
5. Sollmann, T.: A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, ed. 4, Philadelphia, W. B. Saunders Company, 1932, p. 773.

6. Cushing, H.: Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 86.

7. Cushing,[6] pp. 62 and 76.

RESULTS

1. The maximum values to which the blood sugar rose after encephalography can be seen in graph 1. The highest value was 234 mg. per hundred cubic centimeters, in a case of epilepsy in which there was communicating hydrocephalus; the lowest was 100 mg., also in a case of epilepsy. The average maximum value for all cases, except those in which a general anesthetic was given or struggling occurred during the procedure, was 152 mg. There was a tendency for the values to decrease as the age increased. Values in the age group of from 10 to 20 years were considerably higher than the values in other groups.



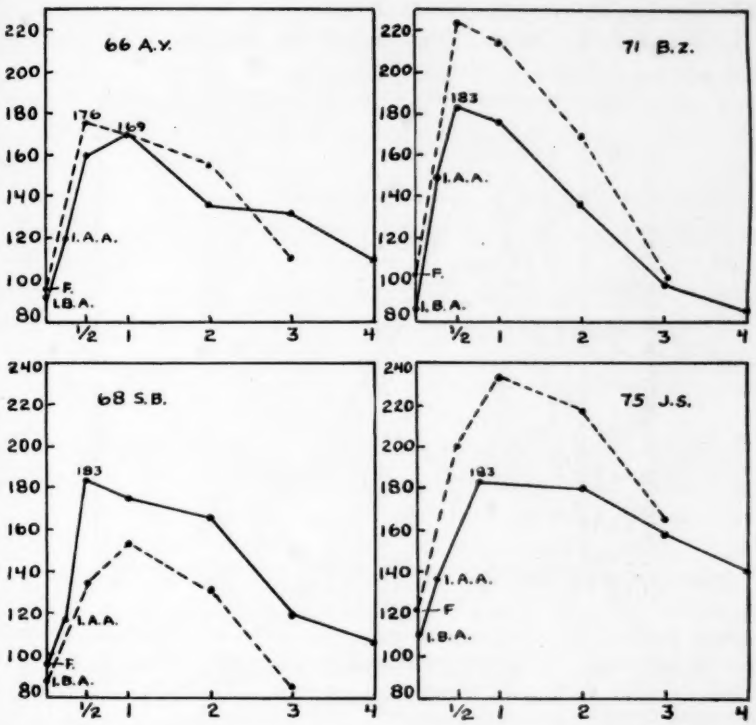

Graph 2.—Curves for blood sugar taken after encephalography under the following conditions:

(*1*) epilepsy (30 cases); (*2*) miscellaneous neurologic disturbances (post-trauma; encephalitis, cerebral thrombosis, etc., 15 cases); (*3*) epilepsy after administration of 1/100 grain (0.6 mg.) of atropine sulfate before injection of air (13 cases), and (*4*) tumor of the brain (5 cases). In *5* is shown the curve for blood sugar during a dextrose tolerance test in ten of the patients with epilepsy represented by curve *1*.

2. In graph 2 can be seen a comparison of the dextrose tolerance curves (*5*) for ten patients with epilepsy and the blood sugar curves after encephalography obtained for patients with the following conditions: (1) epilepsy, thirty; (2) various neurologic diseases, fifteen; (3) epilepsy after administration of atropine sulfate, thirteen, and (4) tumor of the brain, five. The curves are all similar in type, but not in height. The patients with epilepsy showed the highest curve (170 mg.), and those with tumor of the brain, the lowest (137 mg.). The patients with

epilepsy to whom atropine sulfate was administered showed a level 20 mg. lower than those to whom the drug was not given and had a curve identical with that shown in other neurologic conditions (150 mg.). The dextrose tolerance curve (*5*) shows a maximum level of 158 mg. and occupies an intermediate position in relation to the other curves.

3. In graph 3 can be seen a comparison of the dextrose tolerance curves (broken lines) with the blood sugar curves obtained after

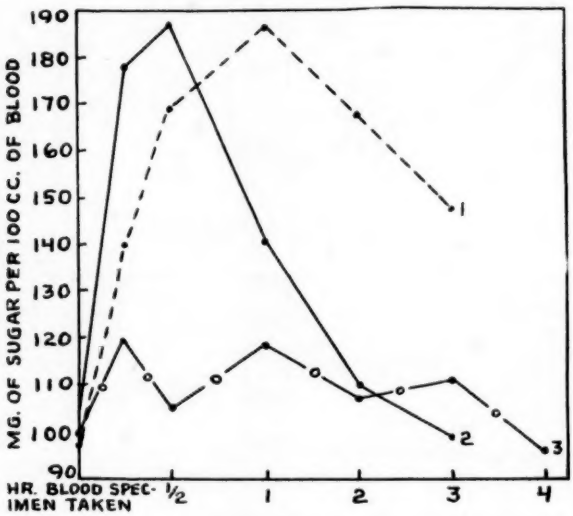



Graph 3.—Graphs showing the typical blood sugar curves obtained after encephalography as compared with the dextrose tolerance curves obtained before encephalography. The abscissas represent the time, expressed in hours, at which the specimen was taken, and the ordinates, the number of milligrams of sugar per hundred cubic centimeters of blood. The unbroken line indicates the curve obtained after encephalography; the broken line, the dextrose tolerance curve; *I.B.A.*, the point immediately before air was injected; *I.A.A.*, the point immediately after the total amount of air was injected, and *F*, the fasting specimen.

encephalography (unbroken lines). Curves in four typical cases are presented: Patients 66, 71 and 75 had epilepsy, and patient 68 complained of posttraumatic headache. The similarity of both types of curves is striking in all cases.

4. Graph 4 shows the type of curve obtained for: (1) patients with epilepsy who exhibited marked struggling during encephalography; (2) patients to whom ether was administered, and (3) patients with tumor of the brain who underwent ventriculography and received tribromethanol as an anesthetic. The marked rise in blood sugar in the patients who struggled and in those who received ether is evident. Patients subjected to ventriculography showed a low level of the blood sugar.

5. The majority of patients with epilepsy who received from 1/100 to 1/60 grain (0.6 to 16.7 mg.) of atropine sulfate subcutaneously




Graph 4.—Types of blood sugar curves seen after encephalography, under the following conditions: (*1*) struggling during the procedure (5 cases); (*2*) administration of ether during the procedure (2 cases), and (*3*) ventriculography in diagnosis of tumor of the brain (5 cases).

before encephalography exhibited an amelioration in postencephalographic symptoms, such as salivation, perspiration and vomiting. The maximum level of the blood sugar was 150 mg., 20 mg. lower than that in patients with epilepsy who did not receive atropine.

6. The first specimen of urine voided after encephalography was tested for sugar and ketone bodies in fifty-three cases. Only six patients showed glycosuria—four less than 0.2 Gm. per hundred cubic centimeters and two, 0.4 and 0.6 Gm., respectively; the last patients showed peaks for blood sugar up to 200 mg. Acetone was present in the urine in only eight cases, and in only two of these was glycosuria shown (less than 0.2 Gm. in both cases).

SUMMARY

Estimations of the blood sugar following encephalography were made on seventy-five patients, twenty-eight males and forty-seven females; the ages ranged from 10 to 62 years.

The average of the highest values for blood sugar (the peak of each curve) was 152 mg. per hundred cubic centimeters of blood. The highest rise was to 234 mg., and the lowest, to 100 mg. The maximum values were in the 10 to 30 year group, and there was a tendency for the values to decrease as the age of the patients increased. The curves for blood sugar following encephalography fell into the following groups: (1) those in miscellaneous neurologic conditions, with an average rise to 150 mg.; (2) those in tumor of the brain showing the lowest average rise (137 mg.), and (3) those in convulsive disorders, showing the highest average rise (170 mg.).

Although the curves were not of differential diagnostic value in the miscellaneous neurologic conditions, the high values in most cases of epilepsy and the extremely low values in cases of tumor of the brain merit consideration. In corroboration of the findings in epilepsy which point to a more sensitive dextrose-regulating mechanism is the work of Schjøtt,[8] who found that after the usual dextrose tolerance test epileptic patients alone showed a marked rise of dextrose in the cerebrospinal fluid.

The usual curve for the dextrose tolerance of the blood is customarily cited as an index of the production of insulin by the islets of Langerhans.

The remarkable similarity in this study between the usual curve for dextrose tolerance and the curve for blood sugar after encephalography (graph 3) in each patient makes one wonder what the dextrose tolerance test actually demonstrates and suggests a common central mechanism for both procedures.

The effect of subcutaneous doses of atropine sulfate given before encephalography in reducing considerably the reactions during and following this procedure corroborates clinically Cushing's experiments with intraventricular injections of solution of posterior pituitary and atropine sulfate [7] and suggests that the pituitary gland is the regulator of the central cerebral mechanism governing the sugar content of the blood. Attention is called to the report by Reese of a case of latent hypoinsulinism [9] in which diabetic coma developed after encephalography and the patient died. The suggestion is made that a preliminary estimation of blood sugar be made in every case in which encephalography is contemplated.

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8. Schjøtt, A.: Clinical Examination of the Nervous System, ed. 6, Monrad-Krohn, 1935, p. 154.

9. Reese, H., in discussion on Walker, E. A.: Encephalography in Children, Arch. Neurol. & Psychiat. **33**:1380 (June) 1935.

# STUDIES IN DISEASES OF MUSCLE

## I. METABOLISM OF CREATINE AND CREATININE IN PROGRESSIVE MUSCULAR DYSTROPHY

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AND
H. G. WOLFF, M.D.
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Although patients with muscular disease commonly show some abnormality in the metabolism of creatine and creatinine, the significance of this finding is still obscure. In the present investigations the factors influencing the excretion of creatine and creatinine in various types of muscular disease were studied. In addition, an attempt was made to correlate the results with the pathologic processes in these conditions. The present report gives the findings in twenty patients with progressive muscular dystrophy, representing all stages of the disease. In addition, observations were made on ten other patients with this condition. However, for the sake of brevity, the data on the second series are not presented, as the findings were similar to those reported here. In formulating the conclusions on the significance of the changes in the metabolism of creatine and creatinine in progressive muscular dystrophy, the data on both series have been used, as well as those on a previous series of fourteen cases reported by one of us (A. T. M.[1]). Therefore, the conclusions are based on observations on a total of forty-four patients.

### METHODS

In selecting patients for study, proper consideration was given to the existence of other factors that can affect the metabolism of creatine and creatinine, such as fever, carbohydrate privation, infancy, sex and endocrine disturbances, notably exophthalmic goiter.

All the subjects were maintained on a diet free from creatine and creatinine and a constant water intake. The urine collected in exactly twenty-four hour specimens was diluted to the same volume each day. The preformed creatinine and creatine were determined by the method of Folin and Benedict, respectively. For the estimation of the total nitrogen the usual macroprocedure of Kjeldahl was employed. Many of the patients were kept in a special metabolism ward, under the supervision of a trained corps of nurses, and the diet and collections of urine were rigorously supervised.

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From the New York Hospital and the Department of Medicine, the Cornell University Medical College, and the Russell Sage Institute of Pathology.

1. Milhorat, A. T.: Ueber die Behandlung der progressiven Muskeldystrophie, und ähnlicher Muskelerkrankungen mit Glykokoll, Deutsches Arch. f. klin. Med. **174**:487, 1933.

Investigation of the patients was divided into four test periods:

1. Period during which the spontaneous excretion of creatine was estimated.
2. Period during which the amount of creatine in the urine was ascertained when the patients were given 1.32 Gm. of creatine by mouth after an adequate period of control. The ability to retain ingested creatine was thus determined. This retention, expressed in terms of the percentage of the amount of creatine administered, is referred to as the "creatine tolerance."
3. Period during which the amount of creatine in the urine was ascertained when the patients were given amino-acetic acid (usually 20 Gm. per day in two doses of 10 Gm. each) after a second period of control.
4. Period during which the amount of creatine in the urine was ascertained when the patients who were receiving amino-acetic acid were given in addition 1.32 Gm. of creatine. The creatine was given in the morning, a few hours after the administration of amino-acetic acid.

### OUTPUT OF PREFORMED CREATININE

The normal adult man excretes from 1.2 to 1.8 Gm. of creatinine in the urine every twenty-four hours. While there are considerable variations in the output among different persons, the amount eliminated by any one person is constant from day to day, independent of quantitative changes in the total amount of nitrogen eliminated. This observation, originally made by Folin,[2] has been confirmed by all later investigators. Deuel[3] found that with a nitrogen-free diet for sixty-three days the creatinine excretion was remarkably constant (from 0.56 to 0.57 Gm. of nitrogen), although the total urinary nitrogen fell from 7.35 to 1.75 Gm.

The output of creatinine is greater in men with well developed muscles and less in men with small muscles and in women (Shaffer[4]). A person's creatinine excretion is related directly to the total mass and efficiency of the muscle. However, there is no relationship between creatinine excretion and the concentration of creatine in the muscle (Chanutin and Kinard[5]). In fact, the output of creatinine in two persons may be the same, but the percentage concentrations of muscle creatine may be quite different.

The first reported observation of decreased excretion of creatinine in progressive muscular dystrophy was that of Rosenthal,[6] in three cases.

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2. Folin, O.: Laws Governing the Chemical Composition of Urine, Am. J. Physiol. **13**:66, 1905.

3. Deuel, H. J., Jr.; Sandiford, I.; Sandiford, K., and Boothby, W. M.: A Study of Nitrogen Minimum: The Effect of Sixty-Three Days of Protein-Free Diet on the Nitrogen Partition Products in the Urine and on the Heat Production, J. Biol. Chem. **76**:391, 1928.

4. Shaffer, P. A.: The Excretion of Kreatinin and Kreatin in Health and Disease, Am. J. Physiol. **23**:1, 1908.

5. Chanutin, A., and Kinard, F. W.: The Relationship Between Muscle Creatine and Creatinine Coefficient, J. Biol. Chem. **99**:125, 1933.

6. Rosenthal, M.: Handbuch der Diagnostik und Therapie der Nervenkrankheiten, Erlangen, F. Enke, 1870, p. 220.

Shortly afterward, Weiss [7] and Langer [8] reported similar observations. However, it was only after Folin [9] had developed a more accurate method for the estimation of creatinine and creatine that adequate studies could be made. Spriggs [10] and Levene and Kristeller,[11] using Folin's method, confirmed the earlier observations that in progressive muscular dystrophy there is a diminution in the elimination of creatinine. These observations have been further extended and confirmed by numerous investigators: notably, McCrudden and Sargent;[12] Janney, Goodhart and Isaacson;[13] Bürger;[14] Meyer;[15] Gibson and Martin;[16] Harris and Brand;[17] Thomas, Milhorat and Techner;[18] Milhorat;[1]

7. Weiss, N.: Ueber einen Fall von progressiver Muskelatrophie, Wien. med. Wchnschr. **27**:702, 1877.

8. Langer, L.: Ein Fall von ausgebreiteter progressiver Muskelatrophie mit paralytischer Lendenlordose, Deutsches Arch. f. klin. Med. **32**:395, 1883.

9. Folin, O.: Beitrag zur Chemie des Kreatinins und Kreatins im Harne, Ztschr. f. physiol. Chem. **41**:223, 1904.

10. Spriggs, E. I.: On the Excretion of Creatinin and Uric Acid in Some Diseases Involving the Muscles, Quart. J. Med. **1**:63, 1907-1908; The Excretion of Creatinin in a Case of Pseudo-Hypertrophic Muscular Dystrophy, Biochem. J. **2**:206, 1907.

11. Levene, P. A., and Kristeller, L.: Factors Regulating the Creatinin Output in Man, Am. J. Physiol. **24**:45, 1909.

12. McCrudden, R. H., and Sargent, C. S.: Hypoglycemia and Progressive Muscular Dystrophy, Arch. Int. Med. **17**:465 (April) 1916; Chemical Changes in the Blood and Urine in Progressive Muscular Dystrophy, Progressive Muscular Atrophy and Myasthenia Gravis, ibid. **21**:252 (Feb.) 1918. McCrudden, F. H.: The Nature of the Pathologic Process in Progressive Muscular Dystrophy, ibid. **21**:256 (Feb.) 1918.

13. Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: The Endocrine Origin of Muscular Dystrophy, Arch. Int. Med. **21**:188 (Feb.) 1918.

14. Bürger, M.: Beiträge zum Kreatininstoffwechsel: II. Die Kreatin- und Kreatininausscheidung bei Störungen des Muskelstoffwechsels, Ztschr. f. d. ges. exper. Med. **9**:361, 1919.

15. Meyer, E. C.: Ueber Kreatin- und Kreatininausscheidung bei Krankheiten, Deutsches Arch. f. klin. Med. **134**:219, 1920.

16. Gibson, R. B., and Martin, F. T.: Some Observations on Creatine Formation in a Case of Progressive Pseudohypertrophic Muscular Dystrophy, J. Biol. Chem. **49**:319, 1921.

17. Harris, M. M., and Brand, E.: Metabolic and Therapeutic Studies in the Myopathies, with Special Reference to Glycine Administration, J. A. M. A. **101**: 1047 (Sept. 30) 1933.

18. Thomas, K.; Milhorat, A. T., and Techner, F.: Untersuchungen über die Herkunft des Kreatins. Ein Beitrag zur Behandlung progressiver Muskelatrophien mit Glykokoll, Ztschr. f. physiol. Chem. **205**:93, 1932; Weitere Untersuchungen über die Herkunft des Kreatins: VII. Mitteilung, ibid. **214**:121, 1933. Milhorat, A. T.; Techner, F., and Thomas, K.: Significance of Creatine in Progressive Muscular Dystrophy, and Treatment of This Disease with Glycine, Proc. Soc. Exper. Biol. & Med. **29**:609, 1932.

Magee;[19] Adams and Power;[20] Kostakow and Slauck;[21] Mettel and Slocum;[22] Reinhold, Clark, Kingsley, Custer and McConnell;[23] Tripoli and Beard;[24] Cuthbertson and Maclachan,[25] and Borst and Möbius.[26]

*Observations.*—The results of the investigation are shown in tables 1 and 2. Comparison of the data with the clinical status of the patients shows that the reduction in the output of preformed creatinine can be slight or considerable, depending on the mass and efficiency of the remaining muscle tissue. In six patients (cases 4, 6, 11, 13, 14 and 15) considerable diminution in the excretion of creatinine was observed. These patients all showed extensive muscular wasting. On the other hand, in four patients (cases 3, 5, 9 and 17), in whom only moderate muscular wasting had occurred, the effect on the output of creatinine was less pronounced. These findings are in agreement with those of all observers whose reports give sufficient data to permit a correlation between the reduction in the creatinine output and the clinical status of the patient. Thus, in a patient showing only moderate impairment of muscular function one of us (A. T. M.) [1] reported the output of creatinine to be only slightly affected (1.11 Gm.), whereas in another patient with advanced muscular disability only 0.06 Gm. of creatinine was excreted in the twenty-four hour period.

Factors other than the functional status of the muscle fibers which determine the output of creatinine are the age and sex of the patient.

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19. Magee, M. C.: Creatine and Creatinine Metabolism in Progressive Muscular Dystrophy: Report of Two Cases and Controls, Am. J. Dis. Child. **43**:19 (Jan.) 1932.

20. Adams, M., and Power, M. H.: Chemical Studies in Patients with Myasthenia Gravis and Progressive Muscular Dystrophy, Proc. Staff Meet., Mayo Clin. **9**:598 (Oct. 3) 1934.

21. Kostakow, S., and Slauck, A.: Die Glykokollbehandung der progressiven Muskeldystrophie, Deutsche med. Wchnschr. **59**:169 (Feb. 3) 1933; Die Glykokollbehandlung der progressiven Muskeldystrophie, Deutsches Arch. f. klin. Med. **175**:25, 1933; Ueber weitere Stoffwechsel-Untersuchungen mit Glykokoll bei progressiver Muskeldystrophie, ibid. **175**:302, 1933.

22. Mettel, H. B., and Slocum, Y. K.: Pseudohypertrophic Muscular Dystrophy: Preliminary Report on the Treatment of Three Cases with Glycine, J. Pediat. **3**:352, 1933.

23. Reinhold, J. G.; Clark, J. H.; Kingsley, G. R.; Custer, R. P., and McConnell, J. W.: The Effects of Glycine (Glycocoll) in Muscular Dystrophy, with Especial Reference to Changes in Structure and Imposition of Voluntary Muscle, J. A. M. A. **102**:261 (Jan. 27) 1934.

24. Tripoli, C. J., and Beard, H. H.: Muscular Dystrophy and Atrophy: Clinical and Biochemical Results Following the Oral Administration of Amino-Acids, Arch. Int. Med. **53**:435 (March) 1934.

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26. Borst, W., and Möbius, W.: Zur Glykokollbehandlung der progressiven Muskeldystrophie, Ztschr. f. klin. Med. **129**:499, 1936.

Thus, in estimating the extent of the decrease in the creatinine output in this disease, comparisons must be made with the average output of normal persons of the same age and sex.

TABLE 1.—*Effects of Ingested Creatine and Amino-Acetic Acid on the Excretion of Urinary Creatinine and Creatine in Progressive Muscular Dystrophy*

| | | Daily Urinary Output | | | | Creatine | | | |
|---|---|---|---|---|---|---|---|---|---|
| Patient | Days in Period | Total Nitrogen, Gm. | Preformed Creatinine, Gm. | Creatine as Creatinine, Gm. | Amino-Acetic Acid per Day, Gm. | Given on First Day of Period, Gm. | Retained, Percentage | Total Creatine Coefficient* | Creatinine Coefficient† |
| Case 1, E. M., male, 14 yr., 37 Kg. | 4 | 6.19 | 0.319 | 0.263 | | | | | |
| | 2 | 7.85 | 0.302 | 0.693 | .. | 1.32 | 14 | 18.5 | 8.62 |
| | 1 | 7.04 | 0.302 | 0.320 | | | | | |
| | 4 | 10.31 | 0.293 | 0.501 | 20 | | | | |
| | 2 | 10.51 | 0.312 | 1.013 | 20 | 1.32 | 0 | | |
| | 6 | 8.31 | 0.312 | 0.532 | 20 | | | | |
| Case 2, D. M., male, 9 yr., 19.5 Kg. | 7 | .... | 0.183 | 0.250 | | | | | |
| | 1 | .... | 0.211 | 0.736 | .. | 1.00 | 27 | | |
| | 3 | .... | 0.170 | 0.215 | .. | .... | .. | 24.7 | 8.77 |
| | 3 | .... | 0.169 | 0.370 | 25 | | | | |
| | 1 | .... | 0.204 | 1.058 | 25 | 1.00 | 9 | | |
| | 3 | .... | 0.197 | 0.365 | 25 | | | | |
| Case 3, L. L., male, 38 yr., 79 Kg. | 2 | 7.95 | 0.858 | 0.181 | | | | | |
| | 2 | 7.82 | 0.964 | 0.270 | .. | 1.32 | 82 | | |
| | 4 | 11.71 | 0.905 | 0.342 | 20 | .... | .. | 15.3 | 10.88 |
| | 2 | 12.18 | 0.973 | 0.766 | 20 | 1.32 | 15 | | |
| Case 4, T. P., female, 13 yr., 37 Kg. | 3 | 5.08 | 0.251 | 0.457 | | | | | |
| | 2 | 5.72 | 0.264 | 0.876 | .. | 1.32 | 16.2 | | |
| | 10 | 8.85 | 0.287 | 0.727 | 20 | .... | .. | 22.2 | 6.78 |
| | 3 | 10.18 | 0.306 | 1.187 | 20 | 1.32 | 0 | | |
| | 1 | 9.67 | 0.274 | 0.806 | 20 | | | | |
| Case 5, R. P., female, 31 yr., 60 Kg. | 6 | .... | 0.672 | 0.123 | | | | | |
| | 3 | .... | 0.708 | 0.388 | 20 | .... | .. | 15.0 | 11.20 |
| Case 6, L. V., female, 27 yr., 50.7 Kg. | 4 | 5.52 | 0.257 | 0.578 | | | | | |
| | 2 | 5.91 | 0.264 | 1.021 | .. | 1.32 | 12 | | |
| | 2 | 8.40 | 0.268 | 0.730 | 10 | .... | .. | 19.1 | |
| | 2 | 8.24 | 0.287 | 1.222 | 10 | 1.32 | 2 | .... | 5.07 |
| Case 7, A. S., female, 29 yr., 54 Kg. | 3 | 7.44 | 0.192 | 0.686 | | | | | |
| | 2 | 7.52 | 0.208 | 1.226 | .. | 1.32 | 0 | | |
| | 4 | 7.57 | 0.199 | 0.699 | .. | .... | .. | 17.0 | 3.61 |
| | 5 | 10.40 | 0.180 | 0.858 | 20 | | | | |
| Case 8, H. R., female, 28 yr., 59 Kg. | 12 | 4.68 | 0.704 | 0.061 | | | | | |
| | 5 | 6.93 | 0.660 | 0.135 | 15 | .... | .. | 16.8 | |
| | 8 | 8.53 | 0.738 | 0.198 | 20 | .... | .. | .... | 12.71 |
| Case 9, H. L., male, 44 yr., 60 Kg. | 2 | 7.54 | 0.976 | 0.067 | | | | | |
| | 2 | 9.62 | 1.057 | 0.377 | .. | 1.32 | 38 | 20.2 | 16.27 |
| Case 10, M. S., female, 18 yr., 51.2 Kg. | 6 | 5.82 | 0.686 | 0.081 | .. | .... | .. | .... | 13.12 |
| | 1 | 6.08 | 0.690 | 0.670 | .. | 1.32 | 42 | | |
| | 11 | 6.64 | 0.677 | 0.232 | | | | | |
| | 4 | 7.84 | 0.663 | 0.360 | 10 | .... | .. | 17.2 | |
| | 1 | 7.73 | 0.658 | 1.056 | .. | 1.32 | 25 | | |
| | 1 | 7.85 | 0.690 | 0.404 | | | | | |

* Milligrams of total creatine (creatine plus creatinine) per kilogram of body weight.
† Milligrams of preformed creatinine per kilogram of body weight.

It has been demonstrated that in progressive muscular dystrophy the diseased muscle fibers may present many variations in size, shape and structure. Muscles containing many such fibers show considerable impairment in function without demonstrable diminution in their total

mass. The atrophied fibers frequently are replaced by fat and connective tissues; in some instances, as in the pseudohypertrophic forms, there is an excessive deposit of fat. Therefore, while patients with the greatest reduction in creatinine output usually have considerable amounts of muscular wasting, the diminution in the elimination of

TABLE 2.—*Effects of Ingested Creatine and Amino-Acetic Acid on the Excretion of Urinary Creatinine and Creatine in Progressive Muscular Dystrophy*

| | | Daily Urinary Output | | | | Creatine | | | |
|---|---|---|---|---|---|---|---|---|---|
| Patient | Days in Period | Total Nitrogen, Gm. | Preformed Creatinine, Gm. | Creatine as Creatinine, Gm. | Amino-Acetic Acid per Day, Gm. | Given on First Day of Period, Gm. | Retained, Percentage | Total Creatine Coefficient* | Creatinine Coefficient† |
| Case 11, C. M., | 2 | 4.74 | 0.192 | 0.803 | .. | 1.32 | 65 | | |
| female, 21 yr., | .. | 5.16 | 0.193 | 0.629 | | | | | |
| 44 Kg. | 7 | 6.10 | 0.202 | 0.654 | .. | .... | .. | 22.5 | 3.64 |
| | 5 | 8.59 | 0.217 | 0.864 | 20 | | | | |
| | 2 | 8.26 | 0.176 | 1.353 | 20 | 1.32 | 2 | | |
| Case 12, B. M., | 10 | 5.67 | 0.504 | 0.453 | .. | .... | .. | 20.6 | 10.00 |
| male, 25 yr., | | | | | | | | | |
| 57 Kg. | | | | | | | | | |
| Case 13, F. B., | 5 | 7.86 | 0.361 | 0.602 | 15 | | | | |
| male, 28 yr., | 8 | 6.76 | 0.335 | 0.503 | | | | | |
| 49 Kg. | 2 | 7.41 | 0.349 | 0.870 | .. | 1.00 | 40 | 15.4 | |
| | 3 | 7.45 | 0.337 | 0.532 | .. | .... | .. | .... | 6.94 |
| Case 14, A. S., | 7 | 6.41 | 0.137 | 0.708 | | | | | |
| male, 22 yr., | 2 | 6.36 | 0.132 | 1.098 | .. | 1.32 | 22 | | |
| 46.5 Kg. | 3 | 6.45 | 0.127 | 0.710 | .. | .... | .. | 24.2 | 3.47 |
| | 6 | 8.03 | 0.125 | 0.856 | 20 | | | | |
| Case 15, E. R., | 1 | 5.07 | 0.209 | 0.345 | | | | | |
| female, 11 yr., | 1 | 4.34 | 0.221 | 0.941 | .. | 1.32 | 40.4 | 23.8 | 6.57 |
| 31.9 Kg. | 1 | 3.34 | 0.216 | 0.314 | | | | | |
| Case 16, C. R., | 1 | 5.08 | 0.246 | 0.446 | | | | | |
| female, 15 yr., | 1 | 5.03 | 0.242 | 1.251 | .. | 1.32 | 19.5 | 17.7 | 5.42 |
| 45.5 Kg. | 1 | 4.32 | 0.240 | 0.539 | | | | | |
| Case 17, W. K., | 7 | 6.75 | 0.884 | 0.294 | | | | | |
| male, 17 yr., | 1 | 6.33 | 0.900 | 0.880 | .. | 1.32 | 40 | | |
| 61 Kg. | 3 | 9.84 | 0.913 | 0.635 | 20 | .... | .. | 22.2 | 14.22 |
| | 2 | 10.28 | 0.891 | 1.146 | 20 | 1.32 | 0 | | |
| Case 18, A. R., | 5 | 5.94 | 0.188 | 0.490 | | | | | |
| male, 10 yr., | 2 | 5.00 | 0.189 | 0.828 | .. | 1.32 | 33 | | |
| 35 Kg. | 5 | 7.30 | 0.206 | 0.502 | 10 | .... | .. | 20.2 | 5.45 |
| | 5 | 6.94 | 0.194 | 0.505 | | | | | |
| Case 19, A. F., | 1 | 7.28 | 0.865 | 0.045 | .. | 1.32 | 60.7 | 15.0 | |
| male, 55 yr., | 1 | 8.40 | 0.865 | 0.438 | .. | .... | .. | .... | 12.35 |
| 70 Kg. | | | | | | | | | |
| Case 20, V. F., | 1 | 9.74 | 0.853 | 0.284 | | | | | |
| male, 25 yr., | 1 | 9.18 | 0.853 | 0.783 | .. | 1.32 | 50 | 18.0 | 13.12 |
| 65 Kg. | | | | | | | | | |

* Milligrams of total creatine (creatine plus creatinine) per kilogram of body weight.
† Milligrams of preformed creatinine per kilogram of body weight.

creatinine is often greater than the apparent reduction in the muscle mass would indicate (case 7 in this series and patient G. G. in the series reported by one of us A. T. M.).[1]

In general, then, Shaffer's observation that the creatinine output is proportional to the muscular mass appears to be true, except that in patients with muscular disease the creatinine output appears to be an

expression of the amount of efficiently functioning muscle tissue rather than the amount of muscle per se.

Unfortunately, no method is available for determining the absolute loss of muscle tissue. The reduction in total body weight cannot be employed because of the fatty tissue changes in the muscle sites or in the subcutaneous deposits following limited activity. The "creatinine coefficient" as employed by many workers is the number of milligrams of creatinine or of creatinine nitrogen eliminated per kilogram of body weight. The first method of expressing the creatinine coefficient (in terms of creatinine) has been used in this report. In tables 1 and 2 the creatinine coefficients for the patients in this series have been computed. Patients in whom extensive muscular wasting had occurred showed the lowest coefficients. Thus, while the normal subject M. A. (table 3) had a coefficient of 24.78, patient W. K. (case 17, table 2), who showed a moderate degree of muscular wasting, had a coefficient of 14.22. In patients F. B. (case 13) and L. V. (case 6), with considerable wasting and functional disability of the muscles, the coefficients were only 6.94 and 5.07, respectively.

Thus, in patients with progressive muscular dystrophy there is a progressive reduction in the creatinine output and in the creatinine coefficient that is proportional to the loss in mass and functional capacity of the muscles.

### OUTPUT OF CREATINE

The normal adult man eliminates considerable amounts of creatinine in the urine but no creatine, or only minimal amounts. By infants and children large amounts of creatine are excreted normally, and in women, notably during pregnancy, a moderate degree of creatinuria is not uncommon.

In disease affecting the muscles, including exophthalmic goiter, creatinuria is often present, even when the patients are maintained on a creatine-free diet.

Levene and Kristeller [11] made the important discovery that patients with progressive muscular dystrophy excrete fairly large amounts of creatine. The studies were extended by McCrudden and Sargent; [12] Janney, Goodhart and Isaacson; [13] Bürger; [14] Meyer; [15] Gibson and Martin; [16] Brand, Harris, Sandberg and Ringer; [27] Harris and Brand; [17] Thomas, Milhorat and Techner; [18] Milhorat; [1] Magee; [19] Adams and Power; [20] Kostakow and Slauck; [21] Chanutin, Butt and Royster; [28] Mettel and Slocum; [22] Reinhold, Clark, Kingsley, Custer

27. Brand, E.; Harris, M. M.; Sandberg, M., and Ringer, A. I.: Studies on the Origin of Creatin, Am. J. Physiol. **90**:296, 1929.

28. Chanutin, A.; Butt, H. R., and Royster, L. I.: A Study of Progressive Pseudohypertrophic Muscular Dystrophy in Children After the Administration of Glycine and Creatin, J. Biol. Chem. **100**:xxvi, 1933.

and McConnell;[23] Tripoli and Beard;[24] Cuthbertson and Maclachan,[25] and Borst and Möbius.[26] All these investigators found creatinuria in progressive muscular dystrophy. On the other hand, Nedelmann[29] observed no creatinuria in his patient.

In this series all the patients with progressive muscular dystrophy excreted creatine. The output of creatine is greater in patients with advanced muscular disability (tables 1 and 2). Also, there is a correlation between the degree of muscular dysfunction and that of creatinuria in patients of about the same age. Furthermore, a slight muscular defect in children is usually accompanied by greater degree of creatinuria than occurs in adults with a comparable muscular defect.

Most patients studied, either young or adult, come under observation only after the disease has progressed until considerable muscular dysfunction is present. In this series of forty-four patients with progressive muscular dystrophy, thirty-nine were either adults showing considerable muscular weakness and wasting and a moderately large creatine output or young persons who also had serious impairment. However, among young persons marked creatinuria is not unusual, even in health.

The output of creatine is commonly quite large, although adults in the early stage of the disease may excrete only small amounts. Thomas[30] gave data on a patient with progressive muscular dystrophy who was observed by competent clinicians for several years. The patient was an adult in whom the disease had progressed slowly and who had only moderate muscular disability. Small amounts of creatine were excreted. Three cases in this series (cases 8, 9 and 19) were similar to the case reported by Thomas. The patients were adults in whom the progress of the disease was slow and whose muscles appeared to function fairly well. The physical findings and history were typical of progressive muscular dystrophy. Thus, in case 8, table 1, a patient with beginning muscular dystrophy excreted only 0.061 Gm. of creatine daily (on four days the output was 0.03 Gm. or less). Observations for two years disclosed no greater creatine output. In a sister a similar syndrome developed later. Patient A. F. (case 19) showed only slight impairment of muscular function and excreted only 0.045 Gm. of creatine daily. During the year following this observation there appeared to be no increase in the muscular disability, and the creatine output remained unchanged.

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29. Nedelmann, E.: Ueber den Kreatininstoffwechsel bei Muskelatrophie, München. med. Wchnschr. **70**:800 (June 22) 1923.

30. Thomas, K.: Glykokoll in der Therapie, Deutsche med. Wchnschr. **60**: 558 (April 30) 1934.

Our observations and those of Bürger,[14] who found a low output of creatine in three cases, confirm the conclusion of Thomas that in certain patients with progressive muscular dystrophy the creatinuria may be of low magnitude. It appears, therefore, that the level of the spontaneous output of creatine per se is not acceptable evidence for either the existence or the nonexistence of progressive muscular dystrophy, as was implied by Harris and Brand.[17] Nor is it evident, as they suggested, that patients with a low output of creatine belong to a special clinical group, except as they represent early stages of the disease in adult persons. It is difficult to draw conclusions concerning the relation of creatine output and progressive muscular dystrophy. The issue is complicated by the creatinuria in children with this disease. Such children usually have marked creatinuria. This may, however, be the result of at least two factors. First, a large spontaneous output of creatine is normally present in children. This, when added to even moderate amounts of creatine in the urine due to the presence of progressive muscular dystrophy, may result in a large total output. A false impression of the magnitude of the output in muscular dystrophy may thus be gained.

The spontaneous output of creatine in some patients with progressive muscular dystrophy may be no greater than that in many persons with myasthenia gravis or muscular wasting secondary to a lesion in the nervous system. However, it will usually be found that the defect in the metabolism is of a different order. In progressive muscular dystrophy the ability to retain ingested creatine is usually more impaired. The effect of the ingestion of amino-acetic acid on the spontaneous output of creatine is likewise more pronounced. For example (case 10, table 1), a patient with progressive muscular dystrophy had an average daily excretion of 0.081 Gm. of creatine for six days. When exogenous creatine in the amount of 1.32 Gm. was given, only 41 per cent was retained. After the increase in the amount of creatine in the urine due to the exogenous creatine eliminated, the subsequent excretion of creatine continued at a higher level than before (an average of 0.232 Gm.). When 10 Gm. of amino-acetic acid was given daily for four days, the output of creatine was further increased to approximately 0.36 Gm. After the increase in the output of creatine due to the ingestion of amino-acetic acid, the excretion of creatine returned to its former level of 0.232 Gm. In contrast, a patient with myasthenia gravis, who had a spontaneous output of creatine of 0.076 Gm., was similarly given 1.32 Gm. of creatine. She retained 73 per cent. Furthermore, when amino-acetic acid (20 Gm.) was given daily for four days, there was an increase in the excretion of creatine to 0.144 Gm., as compared with that of 0.36 Gm. in the patient with muscular dystrophy.

Since a rise in the elimination of creatine is often accompanied by a fall in the output of creatinine, Harding and Gaebler [31] attempted to express this as a "coefficient" or "index." They computed the "total creatine index" (the number of milligrams of urinary creatine plus creatinine expressed as creatine per kilogram of body weight) of a number of normal children and of patients with progressive muscular dystrophy and exophthalmic goiter. The data may also be expressed in terms of creatinine. They concluded that the coefficient is constant in these conditions and is the same as that determined for normal adults. This view was not supported by further investigations. Whereas many patients with progressive muscular dystrophy show a total creatine coefficient of about the same value, i. e., 23, as that computed by Harding and Gaebler, this finding is by no means universal. As indicated in tables 1 and 2, frequent and large deviations from this value occur. Indeed, it would be surprising if the total creatine coefficient was constant in all cases of progressive muscular dystrophy, since this would imply a reduction in preformed creatinine equivalent to the amount of creatine eliminated. As a matter of fact, the diminution of one component is often not compensated by an increase in the other. Moreover, the index is further invalidated because it is based on the assumption that during loss of weight in progressive muscular dystrophy the relation of the loss of skeletal muscle to the total loss of body weight remains constant. In such patients there are a relatively large loss of skeletal muscle (tissue rich in creatine) and a comparatively slight loss in weight of the rest of the body tissues. In certain cases of progressive muscular dystrophy the figure for the total creatine coefficient seems constant. However, this constancy is more apparent than real. As the ratio between the total creatine coefficients is dependent on the body weight, expressed in kilograms, obviously great variations in the output may occur and yet cause only slight changes in the coefficient. For example, when the weight of the patient is 70 Kg., a change of 0.14 Gm. in the total elimination of creatine will alter the coefficient by 2 only, whereas the same change of 0.14 Gm. in the total elimination of creatine in a patient weighing 35 Kg. might change the ratio by 4. Examination of the data in tables 1 and 2 shows that in progressive muscular dystrophy the amounts of creatine excreted are often not as large as the decrease in creatinine output. For example, patient L. L. (case 3) eliminated amounts of creatinine which were estimated to be about 0.7 Gm. less than those which a healthy normal man of the

31. Harding, V. J., and Gaebler, O. H.: The Constancy of the Creatine-Creatinine Excretion in Children on a High Protein Diet, J. Biol. Chem. **54**:579, 1922.

same age and build would excrete. The creatine output was only 0.181 Gm. Several patients in the present series who excreted only moderate amounts of creatine showed similar discrepancies. In brief, the data of these investigations demonstrated that the total creatine coefficient is not a constant. Therefore, the inference drawn from this assumption, namely, that creatine and creatinine are so intimately associated in the metabolism of muscle that the decrease of one is invariably followed by a corresponding increase in the other, is untenable. Moreover, the contention that the total output of creatine and creatinine is independent of muscle mass is fallacious.

### RETENTION OF INGESTED CREATINE [32]

When creatinine is administered, it is promptly and almost completely excreted (Folin [33]), but the normal organism is capable of retaining considerable amounts of ingested creatine without effect on the urinary constituents (Folin,[33] Klercker [34] and Rose and Dimmitt [35]). Only after the prolonged administration of relatively large amounts of creatine is the output of creatinine increased (Rose and Dimmitt,[35] Benedict and Osterberg [36] and Chanutin [37]). The effect of ingested creatine on the excretion of creatinine appears to be influenced by the amount of protein in the diet (Bollman [38]). Small variations in protein intake have no influence on the amount of creatine in the urine, but wide fluctuations in the amount of protein ingested can affect the level of creatine eliminated, even when the protein contains no creatine and only minimal amounts of amino-acetic acid. Gibson and Martin [16] observed an increase in output of creatine when the dietary protein

32. The ability of the body to retain ingested creatine is referred to in this report as the "creatine tolerance."

33. Folin, O.: The Chemistry and Bio-Chemistry of Kreatin and Kreatinin, Festkrift tillegnad Olof Hammersten, Upsala, C. J. Lundström, 1906, pt. 3, p. 1.

34. af Klercker, K. O.: Zur Frage der Kreatin- und der Kreatininausscheidung beim Menschen, Beitr. z. chem. Phys. u. Path. **8**:59, 1906; Beitrag zur Kenntnis des Kreatins und Kreatinins im Stoffwechsel des Menschen, Biochem. Ztschr. **3**: 45, 1907.

35. Rose, W. C., and Dimmitt, F. W.: Experimental Studies on Creatine and Creatinine: VII. The Fate of Creatine and Creatinine When Administered to Man, J. Biol. Chem. **26**:345, 1916.

36. Benedict, S. R., and Osterberg, E.: Studies in Creatine and Creatinine Metabolism: V. The Metabolism of Creatine, J. Biol. Chem. **56**:229, 1923.

37. Chanutin, A.: The Fate of Creatine When Administered to Man, J. Biol. Chem. **67**:29, 1926.

38. Bollman, J. L.: The Influence of Protein Metabolism on the Conversion of Creatine to Creatinine, J. Biol. Chem. **85**:169, 1929.

was increased from 32 to 75 Gm. One of us (A. T. M.)[1] was able to reduce the creatine output in a patient with progressive muscular dystrophy by the substitution of a diet low in nitrogen for one liberal in protein. That creatine is readily synthesized in the normal organism, and in such amounts as will maintain the concentration in the body at a fairly constant level, has been shown by Chanutin [39a] and Chanutin and Shearer [39b] and others.

Liebig [40] as early as 1847 discovered that creatine is a regular constituent of the striated muscles of all higher animals. As much as 98 per cent of the total creatine in the body is contained in the muscles (Bürger [41]). The percentage of the creatine concentration of the body remains constant under a wide variety of dietary conditions. However, when large amounts of creatine are ingested, the concentration within the body can be increased. Chanutin [39a] fed rats a diet containing 10 per cent of creatine and found after the first day an increase in the creatine concentration of the organism. Continued feeding of the diet rich in creatine had no further effect on the creatine concentration of the body. It is probable that moderate amounts of exogenous creatine can be utilized by the organism in place of the creatine that it ordinarily synthesizes.

Creatine exists in the muscles in combination with phosphoric acid to form the labile compound creatine-phosphoric acid, or "phosphagen" (Eggleton and Eggleton [42] and Fiske and Subbarow [43]). The exothermic breakdown of creatine-phosphoric acid furnishes the energy for muscular contraction. The total amount of creatine-phosphoric acid (expressed in terms of creatine) in the body is probably 140 Gm.

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39. (*a*) Chanutin, A.: Studies on the Creatine and Nitrogen Content of the White Rat After Feeding of a Variety of Diets and After Nephrectomy, J. Biol. Chem. **89**:765, 1930. (*b*) Chanutin, A., and Shearer, L. D.: The Effect of Fasting on the Creatine and Nitrogen Content of the Body and Muscle of the White Rat, ibid. **91**:475, 1931.

40. Liebig, J.: Recherches de chimie animale, Compt. rend. Acad. d. Sc. **24**: 69 and 195, 1847; Ueber die Bestandtheile der Flüssigkeiten des Fleisches, Ann. d. Chem. u. Pharm. **62**:257, 1847.

41. Bürger, M.: Beiträge zum Kreatininstoffwechsel: I. Die Bedeutung des Kreatininkoefficienten für die quantitative Bewertung der Muskelatur als Körpergewichtskomponente, Ztschr. f. d. ges. exper. Med. **9**:262, 1919.

42. Eggleton, P., and Eggleton, G. P.: The Inorganic Phosphate and a Labile Form of Organic Phosphate in the Gastrocnemius of the Frog, Biochem. J. **21**: 190, 1927.

43. Fiske, C. H., and Subbarow, Y.: The Nature of the "Inorganic Phosphate" in Voluntary Muscle, Science **65**:401 (April 22) 1927; Phosphocreatine, J. Biol. Chem. **81**:629, 1929.

(Hahn and Meyer [44]). This is split into its constituents creatine and phosphoric acid and is resynthesized many times a day.

No adequate studies have been made on the mechanism of the retention of exogenous creatine. Benedict and Osterberg [36] administered creatine for seventy days to a dog weighing 15 Kg. and induced retention of 16.38 Gm. If one assumes an average of approximately 2 Gm. of creatine per kilogram, a dog weighing 15 Kg. can retain exogenous creatine amounting to 50 per cent of its own creatine content over this period. Chanutin's subject, a normal man weighing 72 Kg., retained 54.5 Gm. in twenty days, or more than a third of his creatine content (Chanutin [37]). Hahn and Fasold [45] injected creatine into rabbits almost daily for six weeks. Amounts of creatine were retained which, if unaltered, would have increased the creatine content of the animals from 50 to 60 per cent. Thus, whether creatine which is retained by the organism is held in the muscles as such is unknown, but it is probably not retained as creatine-phosphoric acid. Possibly both methods of retention are employed.

A reasonable hypothesis concerning the fate of creatine in the body is that some ingested creatine is immediately utilized in the metabolism of creatine-phosphoric acid but that the remainder, and probably the greater proportion, is retained as such in the muscles. Here it may remain a shorter or longer period until it is either utilized in the metabolism of creatine-phosphoric acid or metabolized in some other manner now unknown. Apparently, the organism is capable of utilizing some of the exogenous creatine in place of the creatine it would otherwise synthesize.

In patients with muscular disease the ability to retain ingested creatine is often impaired. Whereas the normal subjects in this series were able to retain all, or practically all, the test amount of 1.32 Gm. of creatine, many patients in the various groups with muscular disease in the present series of studies excreted varying amounts of the creatine administered. Diminished creatine tolerance in progressive muscular dystrophy has been observed previously by various workers (Levene and Kristeller; [11] Gibson, Martin and Buell; [46] Harris and Brand; [17] Milhorat; [1] Mettel and Slocum; [22] Kostakow and Slauck; [21]

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44. Hahn, A., and Meyer, G.: Ueber die gegenseitige Umwandlung von Kreatin und Kreatinin: IV. Die Entstehung von Kreatinin im Organismus, Ztschr. f. Biol. **78**:91, 1923.

45. Hahn, A., and Fasold, H.: Ueber die gegenseitige Umwandlung von Kreatin und Kreatinin, Ztschr. f. Biol. **83**:283, 1925.

46. Gibson, R. B.; Martin, F. T., and Buell, M. V. R.: A Metabolic Study of Progressive Pseudohypertrophic Muscular Dystrophy and Other Muscular Atrophies, Arch. Int. Med. **29**:82 (Jan.) 1922.

Reinhold, Clark, Kingsley, Custer and McConnell;[23] Cuthbertson and Maclachlan;[25] Adams, Power and Boothby,[47] and Kostakow[48]).

*Observations.*—The seventeen patients in the present series (tables 1 and 2) on whom studies of creatine tolerance were made showed impaired ability to retain ingested creatine. The percentage retention varied from 82 to 12. The lowest retention was displayed by patients with extensive wasting of the muscles. On the other hand, impairment in the creatine tolerance was not always proportional to the level of spontaneous output of creatine. Thus, in case 3, in which there was a spontaneous elimination of 0.181 Gm. of creatine, 82 per cent of the creatine was retained, while in case 10, in which there was an output of 0.081 Gm. of creatine, the percentage of retention was only 42. Patients showing the least impairment of creatine tolerance were adults in the earlier stages of the disease. With further progress of the disease the creatine tolerance was progressively lowered. Thus, in moderately advanced stages, e. g., in cases 10 and 17, the creatine tolerance was usually from about 40 to 50 per cent. In far advanced stages 100 per cent of the ingested creatine may be excreted (Milhorat[1] and Kostakow and Slauck[21]). In some instances the level of the output of creatine was raised for a few days after the administration of creatine. If all this "extra creatine" is considered as having come from the exogenous creatine, excretion of over 100 per cent may occur (Milhorat[1]).

As has been discussed previously, some patients with progressive muscular dystrophy show excretion of only small amounts of creatine; yet the ability to retain exogenous creatine can be definitely impaired. Thus, the creatine tolerance test is a better index of the extent of the metabolic defect than is the level of the spontaneous output of creatine. Furthermore, in instances in which the effect of exogenous creatine on the amount of creatine in the urine persists for several days, the spontaneous output of creatine is usually lower than is observed in other patients with a comparable amount of muscular dysfunction. For example, in case 10, during an initial period of six days as a control, the spontaneous output of creatine was only 0.081 Gm. daily. After the ingestion of 1.32 Gm. of creatine the amount of creatine in the urine was increased for two days (average 0.67 Gm.) and then fell

47. Adams, M.; Power, M. H., and Boothby, W. M.: The Influence of Glycine on the Excretion of Creatine and Creatinine, Am. J. Physiol. **111**:596, 1935.

48. Kostakow, S.: (*a*) Beitrag zur Glykokollbehandlung der neuralen Muskelatrophie und dystrophischen Myotonie, Med. Klin. **30**:1127 (Aug. 24) 1934; (*b*) Ueber Spontankreatinurie bei Nervenerkrankungen, Deutsches Arch. f. klin. Med. **178**:387, 1936.

to a new level of 0.232 Gm., at which it remained for the rest of the period of observation (four months). This new level of creatine output appeared to be equivalent to the amount of creatine in the urine usually observed in other patients with similar amounts of muscular dysfunction. The former level of 0.081 Gm. was lower than that in other patients with comparable amounts of muscular wasting. It happened that this patient had taken 20 Gm. of amino-acetic acid daily for about five months, up to four or five months before the present studies were made. During the several months preceding her admission to the hospital she had lived on a practically creatine-free diet. Whether the lowered excretion of creatine was the result of prolonged ingestion of amino-acetic acid and a creatine-free diet is not known.

One of us (A. T. M.[1]) observed that in some patients the prolonged administration of amino-acetic acid was followed by lowering of the spontaneous output of creatine and improvement in the creatine tolerance. These changes sometimes persisted for a few months. Kostakow and Slauck [21] have confirmed the findings. They observed in their patient a lowered amount of creatine in the urine and increase in the retention of exogenous creatine for about six weeks of a period during which no amino-acetic acid was given, following the administration of amino-acetic acid for four months. After this period the amount of creatine in the urine and the creatine tolerance slowly returned to the values observed before the administration of amino-acetic acid. An explanation of the effects observed in case 10 is as follows: Since the patient lived on a practically creatine-free diet, the "burden" of metabolizing exogenous creatine was unusual. It was not until this far greater load of creatine was imposed on the muscles by the creatine tolerance test that the amount of creatine in the urine returned to its former level. Subsequent repeated administrations of creatine, even in amounts of 7.92 Gm., had no further effect on the spontaneous elimination of creatine.

Usually the greater part of the "extra creatine" following a creatine tolerance test is excreted in from twenty-four to forty-eight hours. In the data presented in this report, the creatine output for the two days immediately following the administration of creatine was averaged and used for the computation of the percentage retention. In the instances, however, in which the amount of creatine in the urine returned to its former level on the second day, the values for the first day only were used in expressing the creatine tolerance.

In progressive muscular dystrophy the impairment in the creatine tolerance is usually greater than that in patients with comparable amounts of muscular wasting following a lesion of the nerves or the spinal cord.

Even when the spontaneous elimination of creatine in the last group is as high as that observed in some patients with progressive muscular dystrophy, the creatine tolerance is likely to be normal or only slightly affected, whereas in progressive muscular dystrophy a distinctly subnormal creatine tolerance is the rule. Exceptions will be discussed later.[48c]

### EFFECT OF AMINO-ACETIC ACID ON THE OUTPUT OF CREATINE AND CREATINE TOLERANCE

Amino-acetic acid ("glycine," "glycocoll") is the simplest of the amino-acids and can be synthesized readily by normal mammals (Lewinski [49] and McCollum and Hoagland [50]). Its rôle as a probable precursor of creatine is indicated by the increase in the creatine in the urine following its ingestion in patients with progressive muscular dystrophy. Gibson and Martin [16] observed that the administration of gelatin to a patient with progressive muscular dystrophy was followed by an increase in the creatine output. They made no suggestions as to what constitutent of the gelatin might be responsible for this effect. Brand, Harris, Sandberg and Ringer [27] showed that of the various amino-acids which they investigated amino-acetic acid alone increased the amount of creatine in the urine of such patients. They found that the other amino-acids were entirely, or almost entirely, without effect on the creatine output.

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48c. After the completion of the manuscript of this report, T. Espersen and A. Thomsen (A Study of the Creatine and Creatinine Metabolism in Patients with Progressive Muscular Dystrophy During Treatment with Glycine (Glycocol), Acta med. Scandinav. **92**:39, 1937) published their observations on the output of creatine and creatinine in progressive muscular dystrophy. These authors failed to use diets free from creatine and creatinine and, in consequence, found large fluctuations in the daily elimination of these substances. The employment of the proper diet is a simple and necessary procedure, and this condition should be observed in all studies on the metabolism of creatine and creatinine in patients. A satisfactory diet is one that is free from meat, fish and meat products, such as soup.

It is apparent that patients whose creatine tolerance is low and who excrete a considerable portion of an ingested dose of creatine will likewise excrete much of the creatine of a diet containing meat or meat products. Since the amounts of creatine and creatinine in diets containing meat usually are variable and are unknown, the observations on the output of patients studied under these unsatisfactory conditions are misleading.

49. Lewinski, J.: Ueber die Grenzen der Hippursäurebildung beim Menschen, Arch. f. exper. Path. u. Pharmakol. **58**:397, 1908.

50. McCollum, E. V., and Hoagland, D. R.: Studies on the Endogenous Metabolism of the Pig as Modified by Various Factors: III. The Influence of Benzoic Acid on the Endogenous Nitrogen Metabolism, J. Biol. Chem. **16**:321, 1913.

Tripoli and Beard [24] reported an increase in the excretion of creatine in patients with progressive muscular dystrophy following the administration of glutamic acid. These observations were at variance with those of Brand and his co-workers [51] and Thomas, Milhorat and Techner,[18] who found that this amino-acid is without effect on the creatine in the urine. Weber [52] has recently reported that after the ingestion of amino-acetic acid by patients with progressive muscular dystrophy there is an increase not only in the output of creatine but in the excretion of guanidine-acetic acid (glycocyamine). Since guanidine-acetic acid is probably an intermediate product in the synthesis of creatine from amino-acetic acid, it is likely that the increased excretion of creatine represents an actual increase in the amount of creatine produced. Thomas, Milhorat and Techner [18] observed that the ingestion of amino-acetic acid was always followed by an increase in the creatine in the urine in progressive muscular dystrophy and amyotonia congenita and in a patient with peroneal muscular atrophy of the Charcot-Marie type. On the other hand, the creatine output was unchanged in their patients with wasting of the muscles secondary to disease of the nervous system. It was suggested that this effect of amino-acetic acid might be an aid in the clinical differentiation of the different types of muscular disease. Kostakow [48b] has recently reported similar observations on fifty patients with various types of muscular involvement. In the present studies the factors influencing this effect of amino-acetic acid have been investigated. These will be discussed here and in subsequent reports of this series.

*Normal Subjects.*—The ingestion of amino-acetic acid by normal adult men was without effect on the elimination of either creatinine or creatine. Even when amounts as great as 100 Gm. were taken by M. A., the creatinine output continued extraordinarily constant, and no creatinuria was induced (table 3). Furthermore, no effect on the creatine tolerance could be demonstrated. The complete retention by subject M. A. of the 1.32 Gm. of creatine administered, even when 50 Gm. of amino-acetic acid was ingested, suggests considerable ability on the part of the normal muscles to hold exogenous creatine.

*Progressive Muscular Dystrophy.*—The fourteen patients in the group who were given amino-acetic acid showed increased excretion of creatine (tables 1 and 2). The increase in creatine in the urine bore no direct relationship to either the level of the spontaneous output of

51. Brand, E.; Harris, M. M.; Sandberg, M., and Lasker, M. M.: Further Studies on the Origin of Creatine, J. Biol. Chem. **87**:ix, 1930. Brand and others.[27] Harris and Brand.[17]

52. Weber, C. J.: Isolation of Glycocyamine from Urine, Proc. Soc. Exper. Biol. & Med. **32**:172, 1934.

creatine or the creatine tolerance. The absolute increase in the creatine output varied from 0.099 Gm., in case 13, in which 15 Gm. of amino-acetic acid was given, to 0.341 Gm. in case 17, in which the intake of amino-acetic acid was 20 Gm. daily. The percentage increase in the creatine in the urine varied from 20 per cent, in case 13, to 214 per cent, in case 8. The percentage increase was greater in patients with the lower levels of spontaneous output of creatine.

In all the patients studied the retention of ingested creatine was less when the creatine was given while the patient was simultaneously

TABLE 3.—*Effects of Ingested Creatine and Amino-Acetic Acid on the Excretion of Urinary Creatinine and Creatine in Normal Adults* *

| Subject | Days in Period | Daily Urinary Output | | | Amino-Acetic Acid per Day, Gm. | Creatine | |
|---|---|---|---|---|---|---|---|
| | | Total Nitrogen, Gm. | Preformed Creatinine, Gm. | Creatine as Creatinine, Gm. | | Given, Gm. | Retained, Percentage |
| M. A., male, 33 yr., 77 Kg. | 4 | 8.76 | 1.904 | 0 | | | |
| | 2 | 8.50 | 1.915 | 0 | .. | 1.32 | 100 |
| | 4 | 8.51 | 1.835 | 0 | | | |
| | 4 | 11.02 | 1.824 | 0 | 20 | | |
| | 3 | 15.10 | 1.841 | 0 | 50 | | |
| | 2 | 21.97 | 1.870 | 0 | 100 | | |
| | 1 | ..... | 1.800 | 0 | 60 | | |
| | 2 | 12.67 | 1.800 | 0 | 25 | | |
| | 1 | 12.26 | 1.800 | 0 | 50 | 1.32 | 100 |
| | 1 | 11.86 | 1.826 | 0 | | | |
| P. B., male, 29 yr., 74 Kg. | 2 | 9.18 | 1.712 | 0.092 | | | |
| | 1 | 7.62 | 1.633 | 0.055 | .. | 1.32 | 100 |
| | 4 | 7.42 | 1.640 | 0 | | | |
| | 1 | 6.49 | 1.629 | 0.060 | .. | 1.32 | 100 |
| | 1 | 5.84 | 1.562 | 0 | | | |
| | 2 | 8.49 | 1.590 | 0 | 20 | | |
| | 1 | 9.65 | 1.645 | 0 | 20 | 1.32 | 100 |
| | 1 | 11.48 | 1.621 | 0 | 20 | | |
| C. R., male, 26 yr., 60 Kg. | 2 | 10.96 | 1.640 | 0.017 | | | |
| | 1 | 10.13 | 1.680 | 0.050 | .. | 1.32 | 100 |
| | 1 | 11.19 | 1.680 | 0 | | | |
| W. A., male, 56 yr., 60 Kg. | 1 | 13.50 | 1.610 | 0 | | | |
| | 1 | 14.40 | 1.648 | 0.152 | .. | 1.32 | 84.8 |

* Data on normal infants and children are given by Marples and Levine: (Creatinuria of Infancy and Childhood: I. Normal Variations; Creatine Tolerance Tests and the Effect of Amino-Acetic Acid in Normal Infants, Am. J. Dis. Child. **51**: 30 [Jan.] 1936).

receiving amino-acetic acid. The effect on the creatine tolerance could be demonstrated best when the creatine was ingested not less than two or three hours, or more than twelve hours, after the amino-acetic acid was administered. Thus, when the creatine was given at the same time as or at too long an interval after the amino-acetic acid, no effect on the creatine tolerance was observed (cases 10 and 11). In both these instances amino-acetic acid had been given about eighteen hours before the creatine tolerance test. However, when the creatine was given a few hours after the amino-acetic acid, the creatine tolerance was reduced in case 11 from 55 to 2 per cent and in case 10 from 42 to 25 per cent. In three other patients who had not been given amino-acetic acid pre-

viously, no effect on the retention of exogenous creatine was observed when amino-acetic acid and creatine were administered at the same time. This delay in the effect of amino-acetic acid on the creatine tolerance is probably due to the time required for the absorption of the amino-acid and its possible conversion to creatine.

It would seem unreasonable that amino-acetic acid should decrease the retention of ingested creatine, since this amino-acid improves muscular function in some patients with progressive muscular dystrophy and myasthenia gravis—diseases associated with already impaired creatine tolerance. A plausible explanation for the lowered creatine tolerance after the administration of amino-acetic acid is as follows: It may be due to the action of amino-acetic acid as a precursor of creatine. After amino-acetic acid has been administered, the creatine content of the muscles rises, and in consequence less of the ingested creatine is retained.[53]

In table 4 the effect of amino-acetic acid and that of ingested creatine are compared. During two periods in which the nitrogen intake was kept constant the creatine in the urine was increased to the same level, first by amino-acetic acid and then by ingested creatine. Two hours after the administration of either the amino-acetic acid or the creatine, the creatine tolerance was determined. In one patient (case 7) 20 Gm. of protein given in addition to the basic diet of 45 Gm. did not affect the spontaneous output of creatine appreciably. However, the creatine tolerance was reduced slightly. On a diet containing 45 Gm. of protein the patient retained 14 per cent of the ingested creatine. When large amounts of protein were given, no exogenous creatine was retained. In two patients with an intake of from 50 to 70 Gm. of protein there was no significant difference in either the level of the spontaneous output of creatine or the creatine tolerance. When 20 Gm. of amino-acetic acid was added to the 50 Gm. of protein in the diet, the creatine output was increased and the creatine tolerance diminished. Furthermore, in case 10, when small amounts of creatine (0.377 Gm.) were added to the diet containing 70 Gm. of protein and the creatine output was adjusted in this manner to the same level as that observed when 50 Gm. of protein plus 20 Gm. of amino-acetic acid was given, the creatine tolerance was correspondingly lowered. Thus, it is conceivable that amino-acetic acid acts as a stimulant to the creatine

53. This explanation requires further confirmatory evidence. Contrary to the findings of Beard and Barnes (The Influence of Feeding Proteins, Amino Acids, and Related Substances upon Creatine-Creatinine Metabolism, J. Biol. Chem. **94**: 49, 1931), Bodansky (Comparison of Glycine and Guanido-Acetic Acid as Precursors of Creatine, J. Biol. Chem. **115**:641, 1936) was unable to demonstrate any increase in the creatine content of the muscles after feeding amino-acetic acid.

mechanism, but it appears more likely that the effect of amino-acetic acid on creatine tolerance is due to its action as a precursor of creatine.

Large increments in the nitrogen intake can increase the creatine in the urine in patients with progressive muscular dystrophy (Levene and Kristeller [11]) and in children (Denis and Kramer [54]), but they do not induce creatinuria in normal men and women (Rose, Dimmitt and Bartlett [55]).

TABLE 4.—*Effects of Replacement of Protein Nitrogen with Amino-Acetic Acid on the Creatine Tolerance and Output of Creatine in Progressive Muscular Dystrophy: Comparison of the Effects of Amino-Acetic Acid and Creatine on the Creatine Tolerance (with Equivalent Nitrogen Intake and Creatine Output)*

| | | | | | Daily Urinary Output | | | Creatine | |
|---|---|---|---|---|---|---|---|---|---|
| Patient | Days in Period | Dietary Protein per Day, Gm. | Amino-Acetic Acid per Os Daily, Gm. | Nitrogen Intake Daily, Gm. | Total Nitrogen, Gm. | Preformed Creatinine, Gm. | Creatine as Creatinine, Gm. | Given First Day of Period, Gm. | Retained, Percentage |
| Case 17 | 3 | 70 | .. | 11.2 | 9.34 | 0.869 | 0.301 | | |
| W. K. | 1 | 70 | .. | 11.2 | 10.12 | 0.895 | 0.910 | 1.32 | 39 |
| | 7 | 50 | .. | 8.0 | 6.75 | 0.884 | 0.294 | | |
| | 1 | 50 | .. | 8.0 | 6.33 | 0.900 | 0.880 | 1.32 | 40 |
| | 3 | 50 | 20 | 11.7 | 9.84 | 0.913 | 0.635 | | |
| | 2 | 50 | 20 | 11.7 | 10.28 | 0.891 | 1.146 | 1.32 | 0 |
| Case 10 | 3 | 50 | .. | 8.0 | 5.94 | 0.655 | 0.196 | | |
| M. S. | 2 | 50 | .. | 8.0 | 6.66 | 0.633 | 0.548 | 1.32 | 30 |
| | 4 | 50 | 20 | 11.7 | 9.89 | 0.636 | 0.423 | | |
| | 2 | 50 | 20 | 11.7 | 9.76 | 0.625 | 0.838 | 1.32 | 17 |
| | 2 | 50 | 20 | 11.7 | 9.50 | 0.628 | 0.418 | | |
| | 6 | 70 | .. | 11.7 | 7.92 | 0.647 | 0.225 | | |
| | 2 | 70 | .. | 11.2 | 8.12 | 0.650 | 0.606 | 1.32 | 33 |
| | 5 | 70 | * | 11.3 | 8.76 | 0.652 | 0.388 | | |
| | 4 | 70 | † | 11.3 | 8.59 | 0.652 | 0.433 | | |
| | 2 | 70 | † | 11.3 | 8.33 | 0.645 | 0.484 | 1.32 | 17 |
| | 2 | 70 | † | 11.3 | 8.72 | 0.648 | 0.489 | | |
| Case 7 | 3 | 65 | .. | 10.4 | 7.44 | 0.192 | 0.686 | | |
| A. S. | 2 | 65 | .. | 10.8 | 7.52 | 0.208 | 1.226 | 1.32 | 0 |
| | 4 | 65 | .. | 10.4 | 7.57 | 0.199 | 0.699 | | |
| | 4 | 65 | 5 | 11.3 | 8.59 | 0.192 | 0.708 | | |
| | 7 | 65 | 8 | 11.9 | 8.42 | 0.188 | 0.765 | | |
| | 5 | 65 | 20 | 14.1 | 10.40 | 0.180 | 0.858 | | |
| | 5 | 45 | .. | 7.2 | 5.56 | 0.193 | 0.672 | | |
| | 5 | 45 | 20 | 10.9 | 8.65 | 0.199 | 0.827 | | |
| | 8 | 45 | .. | 7.2 | 5.19 | 0.199 | 0.684 | | |
| | 2 | 45 | .. | 7.6 | 5.03 | 0.201 | 1.121 | 1.32 | 14 |
| | 2 | 45 | .. | 7.2 | 4.96 | 0.198 | 0.671 | | |

* In place of amino-acetic acid, 0.293 Gm. of creatine was given daily.
† Creatine, 0.377 Gm. was given daily to adjust the creatinuria to the level induced by 20 Gm. of amino-acetic acid.

Moreover, large increases in nitrogen intake decrease the creatine tolerance. However, the effects of amino-acetic acid cannot be ascribed

54. Denis, W., and Kramer, J. G.: The Influence of Protein Intake on Creatine Excretion in Children, J. Biol. Chem. **30**:189, 1917.

55. Rose, W. C.; Dimmitt, J. S., and Bartlett, H. L.: Experimental Studies on Creatine and Creatinine: VIII. The Alleged Exogenous Origin of Urinary Creatine in the Protein of the Diet, J. Biol. Chem. **34**:601, 1918.

to changes in the nitrogen intake. It has been demonstrated that the admistration of amino-acetic acid is followed by increase in the creatine output in patients with progressive muscular dystrophy, even when the total nitrogen intake remains constant (Brand, Harris, Sandberg and Ringer [27]). Other amino-acids did not give this effect. Furthermore, when a comparison was made of the effects of equivalent amounts of amino-acetic acid and protein (table 4), it was observed that the addition of 20 Gm. of protein to an already adequate diet was practically without effect on either the degree of creatinuria or the creatine tolerance. On the other hand, the addition of 20 Gm. of amino-acetic acid to the same diet increased the creatine output from 0.294 to 0.635 Gm. and decreased the retention of ingested creatine from 40 per cent to zero (case 17).

Observations on the increase in creatine output following administration of amino-acetic acid have been reported (Brand, Harris, Sandberg and Ringer;[27] Thomas, Milhorat and Techner;[18] Milhorat;[1] Chanutin, Butt and Royster;[28] Adams, Power and Boothby;[47] Kostakow and Slauck;[21] Harris and Brand;[17] Mettel and Slocum;[22] Mettel;[56] Beard, Tripoli and Andes;[57] Tripoli and Beard,[24] and Cuthbertson and Machlachlan[25]). Thomas, Milhorat and Techner[18] have shown that in some cases of progressive muscular dystrophy the administration of amino-acetic acid for long periods is accompanied by a gradual increase in the creatinine output and a gradual fall in the creatine in the urine. After a few months the amount of creatine in the urine was no greater, or even less, than that observed before the administration of amino-acetic acid. When amino-acetic acid was discontinued, the creatine in the urine fell to a new low level. Accompanying these changes in the creatine output, the creatine tolerance increased.

These observations on the creatine output and the creatine tolerance have been confirmed entirely or in part by more recent workers (Kostakow and Slauck,[21] Cuthbertson and Machlachlan[25] and Mettel and Slocum[22]) in patients with progressive muscular dystrophy and in those with muscular disease subsequent to lesions of the peripheral nerves. The effects of amino-acetic acid administered for long periods must be distinguished from those observed during short periods. It is with the effects of the latter that the present report deals.

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56. Mettel, H. B.: Pseudohypertrophic Muscular Dystrophy, J. Pediat. **5**: 359, 1934.

57. Beard, H. H.; Tripoli, C. J., and Andes, J. E.: The Diagnostic and Prognostic Significance of the Creatin-Creatinin Metabolism in Various Myopathies Before and After Amino-Acid Therapy, Am. J. M. Sc. **188**:706, 1934.

### EFFECT OF EQUIVALENT AMOUNTS OF AMINO-ACETIC ACID AND PROTEIN ON URINARY NITROGEN AND NITROGEN BALANCE

The urinary output of nitrogen and the nitrogen balance following the ingestion of amino-acetic acid and of protein were determined. In seven experiments on six patients amino-acetic acid and protein of equivalent nitrogen contents were given in addition to a constant basic diet, and their effects were compared. The elimination of nitrogen following the ingestion of amino-acetic acid was slightly higher than when a complete protein was given. The difference was greater than could be accounted for by the difference in the amounts of creatine excreted. Although amino-acetic acid probably plays a significant rôle in the chemical metabolism of the muscle, it appears that only a small part of that ingested is utilized in the muscle. A large part of the amino-acetic acid administered must be metabolized in other ways. The ability of the body to utilize protein more completely than amino-acetic acid would offer an explanation of the differences in the nitrogen output and the nitrogen balance.

### CONVERSION OF CREATINE INTO CREATININE IN THE BODY

Folin [33] observed no increase in the elimination of creatinine after the ingestion of 4.4 Gm. of creatine. However, the excretion of urinary creatinine is increased when normal subjects and dogs ingest large amounts of creatine for long periods (Chanutin [37] and Benedict and Osterberg [36]). In fact, an increased creatinine output even after small single doses of creatine (from 2 to 3 Gm.) has been reported (Myers and Fine,[58] Rose and Dimmitt [35] and Lyman and Trimby [59]). Some observers have reported that in patients with muscular disease there is an increase in the excretion of creatinine after the ingestion of creatine or amino-acetic acid. Thus, the administration of creatine in patients with progressive muscular dystrophy was followed by an increase in the creatinine output (Levene and Kristeller [11] and Gibson and Martin [16]). Increased creatinine excretion after the ingestion of amino-acetic acid has been observed by Tripoli and Beard [24] in patients with progressive muscular dystrophy. However, most investigators have observed no appreciable change in the creatinine excretion in patients with muscular disease following either amino-acetic acid or the amounts of creatine usually given for studies on creatine tolerance.

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58. Myers, V. C., and Fine, M. S.: The Metabolism of Creatine and Creatinine: VII. The Fate of Creatine When Administered to Man, J. Biol. Chem. **21**:377, 1915; The Influence of the Administration of Creatine and Creatinine on the Creatine Content of the Muscle, ibid. **16**:169, 1913.

59. Lyman, J. F., and Trimby, J. C.: The Excretion of Creatine and Creatinine Parenterally Introduced, J. Biol. Chem. **29**:1, 1917.

In the studies reported here there was no evidence that the amounts of creatine given for the determination of creatine tolerance or that amino-acetic acid given over short periods had any appreciable effect on the excretion of creatinine. Small variations were observed occasionally, but usually they were not significant and rarely exceeded the day to day variations in the creatinine output during the periods used as controls. An occasional increase in the elimination of creatinine was found when large amounts of creatine (5 Gm. or over) were ingested.

In general, it is agreed with Harris and Brand [17] that ingestion of small amounts of creatine, such as are used in studies on creatine tolerance, is without effect on the elimination of creatinine. When large amounts of creatine are ingested, the elimination of creatinine may be increased. The administration of amino-acetic acid over short periods does not affect appreciably the creatinine output, but there is sometimes an increase in the excretion of creatinine after prolonged administration of amino-acetic acid (one of us [A. T. M.][1]).

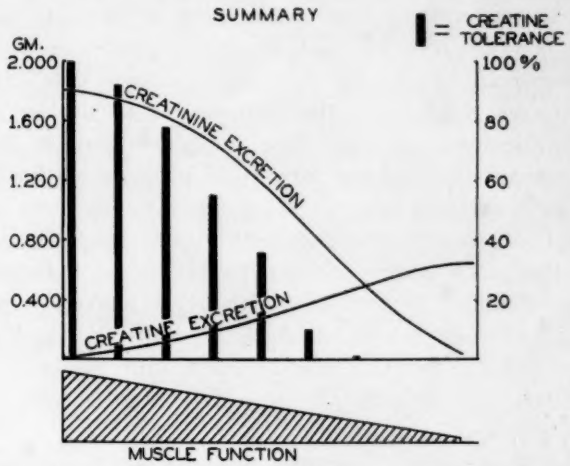
## COMMENT

In the chart are summarized the changes in the excretion of creatine and creatinine and the creatine tolerance that occur in progressive muscular dystrophy.

Examination of the data makes it seem probable that a defect in the metabolism of creatine and creatinine may be taken as an index of the amount of improperly functioning muscle rather than of the amount of wasted muscle. In wasting secondary to disease of the cord, although certain muscle fibers are completely destroyed by disease, others are adequate and function completely. Moreover, in patients with severe wasting subsequent to disease of the nerves there are commonly regions of the body in which the structure and function of the muscles are adequate, and even entirely normal. Under such circumstances, as will be shown in a later report, clearly evident atrophy may be accompanied by only slightly disturbed metabolism of creatine and creatinine. In contrast, primary myopathy may be looked on as the expression of a general disturbance in muscular metabolism which affects all or most of the muscle tissue of the body. Furthermore, the actual enlargement of the muscles in certain myopathies, notably, progressive muscular dystrophy, makes it especially difficult to correlate visible wasting or atrophy with the known defects in metabolism. Hence, the necessity of expressing muscle status in terms of functional capacity rather than of size or postulated structural alterations becomes apparent. It is evident that slight or barely visible atrophy may be accompanied by severe disturbances in the metabolism of creatine and creatinine.

In brief, patients with a generalized defect in the metabolism of muscle may have all the muscle fibers in the body affected chemically without striking visible evidence of wasting until the process has persisted for long periods. On the other hand, patients with striking visible evidence of atrophy may have the bulk of the musculature in a sound state and hence show minimal evidence of disturbance in metabolism.

In this connection a brief discussion of the review of muscular disease by Aring and Cobb [60] is relevant. They supported the concept that muscular disease not subsequent to any known degeneration of the nervous system is characterized by widespread muscular involvement, as compared with muscular defect subsequent to disease of the




Relationship between the changes in muscular function and the metabolism of creatine and creatinine in progressive muscular dystrophy.

anterior horn cells or the peripheral nerves, in which involvement is more specifically localized. Moreover, these authors expressed the opinion that in the muscular diseases which come in infancy the muscular defect is most widespread, while in those coming later in life it appears to be more localized. This generalization, in their opinion, holds for both groups of muscular disease, e. g., the conditions not subsequent to any known degeneration of the nervous system and those subsequent to disease of the anterior horn cells. Since, however, the last group of muscular disorders in infants includes only the Werdnig-Hoffmann type, which is extremely rare, the generalization holds primarily for the muscular diseases not subsequent to known disease of

60. Aring, C. D., and Cobb, S.: The Muscular Atrophies and Allied Disorders, Medicine **14**:77, 1935.

the nervous system. Aring and Cobb also expressed the opinion that the muscular diseases which affect several members of the same generation of a family are those which affect many muscles, often including those of the trunk.

These generalizations seem too sweeping, but if limited to the group of progressive muscular dystrophies they are in accord with the observations described here. Myasthenia gravis, to be sure, is an outstanding exception, since whether it has its onset early or late in life, it may be equally widespread and may run an equally malignant course.

In keeping with the widespread and serious involvement of muscles in the infantile and juvenile forms of progressive muscular dystrophy is the severe disturbance in the metabolism of creatine and creatinine. Not only are the muscular involvement extensive and the disturbance in metabolism severe but the march of the defect in muscular function and metabolism is rapid. In contrast stand the conditions in which the muscular disease appears later in life. The muscular deficiency in these forms progresses slowly, and the disturbances in the metabolism of creatine and creatinine are less. The parallelism between the severity of the muscular disease and the rapidity of progress of the disturbance in metabolism is probably not coincident. Periodic chemical and clinical studies of patients show a correlation between the changes in the metabolism of creatine and creatinine and the clinical status. Patients in whom the muscular disability progresses rapidly show a likewise progressive and rapid impairment in the metabolism of creatine and creatinine. On the other hand, patients in whom there is little change in the functional capacity of the muscles over a year or more exhibit only slight changes in the defect in metabolism.

Thus, the most general inference that emerges from these studies on muscular disease is that disturbances in the metabolism of creatine and creatinine and muscular defects are related and sometimes parallel each other. It must be emphasized that the term muscular defect does not of necessity imply visible wasting, although this may be present. Moreover, it has been demonstrated that in instances in which disease is widespread, notably in muscular diseases not subsequent to any known degeneration of the nervous system, the most serious disturbances in metabolism occur, whereas in instances of muscular defect subsequent to degeneration of the anterior horn cells or peripheral nerves, which is commonly more circumscribed, the disturbances are less. In a later report it will be shown that the exceptions to this general correlation are unusual instances of muscular defect due to nerve lesions which is so widespread as to simulate progressive muscular dystrophy. In brief, there is a parallelism between metabolic disturbances and the total mass of improperly functioning muscle.

SUMMARY

1. Patients with diseases which affect the skeletal muscles commonly have creatinuria, even when they are maintained on a creatine-free diet. Accompanying the creatinuria there is usually diminution in the excretion of creatinine and in the ability of the body to retain ingested creatine (low creatine tolerance).

2. In progressive muscular dystrophy large amounts of creatine are often excreted. The level of the creatine in the urine and the impairment of creatine tolerance are usually related to the amount of muscular disability. In advanced stages of the disease the creatine tolerance can be impaired to the extent that all of an ingested dose of creatine is excreted in the urine as creatine. The amounts of creatinine excreted are diminished and appear to be related to the amount of functioning muscle remaining.

3. The ingestion of amino-acetic acid for short periods is followed by an increase in the creatine in the urine and a further decrease in creatine tolerance. In fact, under these circumstances the amino-acetic acid appears to act as an amplifier of defects in creatine tolerance. Moreover, it is sometimes of use in demonstrating less obvious disturbances in creatine metabolism. Such effects differ greatly from, and are not to be confused with, the results of prolonged ingestion of amino-acetic acid.

4. The effect of amino-acetic acid on the metabolism of creatine in muscular disease, as shown by the amount of creatine in the urine and the creatine tolerance, is out of all proportion to the effect of comparable amounts of nitrogen from sources other than amino-acetic acid and creatine. It is possible that amino-acetic acid acts as a precursor of creatine.

5. In patients with muscular wasting the total creatine coefficient (milligrams of creatine plus creatinine per kilogram of body weight) is not constant but diminishes as the incapacity of the muscle advances.

6. The creatine output and creatine tolerance would appear to be an expression of the total mass of improperly functioning muscle and not, per se, an index of the amount of wasted muscle or the primary site of the disease.

REPORT OF CASES

CASE 1.—E. M., a 14 year old boy, entered the New York Hospital on Aug. 14, 1933, complaining of muscular weakness which had had its onset in infancy. He did not walk until the age of 18 months and had always stumbled and fallen readily. At the age of 3 (1922) he lost all his hair and was bald for a year. Since his earliest attempts at walking he had "waddled." He had always been able to raise his arms above his head, but there was definite weakness of the muscles of the upper portions of the arms and the shoulder girdle. One sister, aged 15, was similarly affected. His past and family history were otherwise irrelevant.

Examination revealed that the patient was short and stocky (weight, from 37 to 38 Kg.) and had abundant hair on the head and pronounced pads of fat on the abdomen, breast and hips. He had flaring scapulae, diminished power in the sternocleidomastoid muscles and weakness of most other muscles of the shoulder girdle and neck. The iliopsoas muscles were also weak. The patient raised himself from the prone to the upright position by lifting his torso with his shoulders and arm muscles, thus "climbing up" on his legs. The muscles of the legs, especially the proximal, were weak but not atrophic. All the muscles were soft and flabby. No sensory defects were noted.

Case 2.—D. M., a 9 year old boy, was admitted to the New York Hospital on Feb. 12, 1933, complaining of difficulty in walking for eighteen months. At the age of 7 (1931) he began to have difficulty in ascending the stairs. This grew progressively worse for six months and then apparently remained unchanged. Six members of the family, including a brother aged 14, a maternal uncle and granduncle and a child of the granduncle, had similar difficulties. In each the onset of the disability had been at the age of from 7 to 8 years. The patient's past personal history was otherwise irrelevant.

Examination revealed weakness of the iliopsoas muscles and the muscles of the lower extremities. The peroneal muscles were weak and showed pseudohypertrophy; the left peroneal group felt "wooden." There was no definite wasting of the muscles of the upper extremities, but the left biceps muscle was weak and there was slight "winging" of the scapulae. The head and neck were not affected. The boy weighed 20 Kg.

Case 3.—L. L., a Jewish business man aged 38, was first observed at the New York Hospital on Dec. 9, 1933. In 1926, at the age of 30, he began to have difficulty in raising his thighs. This gradually became worse, and in 1929 he had difficulty in lifting his feet. In 1932 he entered the Johns Hopkins Hospital, where a diagnosis of progressive muscular dystrophy was made. His mother and three sisters of his mother as well as his mother's father and his four first cousins (on the maternal side) were similarly affected. The family and past personal histories were otherwise noncontributory.

Examination revealed weakness of the iliopsoas muscles and of the muscles of the lower extremities. The peroneal muscles were weak, although the calves were large. The muscles of the left calf were of wooden consistency. There was no definite wasting of the muscles of the upper extremities, but the left biceps muscle was weak and there was slight winging of the scapulae. The patient weighed 79 Kg.

Case 4.—T. P., a 13 year old school girl, entered the New York Hospital in September 1933, complaining of "muscle trouble." This was first noted at the age of 7 (1927) and began with frequent falling when the child was at play. At such times, in order to raise herself again, she had to "roll over on all fours." She had never been able to run as fast as other children and frequently stumbled. By the age of 9 (1929) there was definite weakness of both arms. The weakness of the arms and legs grew progressively worse during subsequent years, and at the time of admission to the hospital the patient could walk only with difficulty. The onset of fatigue was not rapid, but weakness was generalized.

The family history was of interest. A sister aged 25 was totally incapacitated, with the same type of defect. A sister aged 18 was well. The father was living and well and was an extremely muscular man, employed as a steel worker. The past and family histories were otherwise irrelevant.

Examination revealed marked atrophy of the muscles of the shoulders and upper portions of the legs. The patient assumed a slouching or stooping posture

and walked with a waddling gait, with an evident foot drop. She descended steps with difficulty, and ascending was barely possible. She could not raise herself from the prone position or to the erect position if she bent over to touch the floor with her hands. She could stand alone, but with difficulty. There were marked winging of the scapulae and scoliosis. In addition, there was moderate atrophy of the trapezius muscle on both sides, as well as extreme atrophy of the deltoid, pectoralis, serratus, subscapularis, rhomboidus, supraspinatus, infraspinatus and biceps muscles bilaterally. The trapezius, triceps and forearm muscle groups were larger than normal, though weak. There were moderate and symmetrical weakness of the muscles of the lower part of the back and atrophy and weakness of the gluteal, hamstring and anterior tibial muscle groups. The extensor muscles of the thigh were stronger; the gastrocnemius-soleus group was the strongest, though of wooden consistency. The tongue had a tremor and deviated slightly to the right. There was slight, diffuse enlargement of the thyroid. The child weighed 37 Kg.

CASE 5.—R. P., an unmarried woman aged 31, entered the Bellevue Hospital [61] on Dec. 12, 1932, complaining of generalized muscular weakness. At the age of 15 (1916) she had noticed slowly developing weakness of the proximal muscles of the right arm. The process gradually progressed and involved other muscle groups, so that shortly after the left arm was similarly affected. At the age of 21 (1922) the patient began to have difficulty in walking upstairs and in rising from a sitting position. At the age of 24 (1925) walking became difficult because of the increasing weakness and a tendency to fall. The past personal history and family history were irrelevant.

Examination showed generalized weakness and atrophy of proximal muscles, especially of the shoulder and upper part of the arm, with pseudohypertrophy of the deltoid and infraspinatus muscles. The facial muscles were weak and flattened. The gait was waddling, and on arising from a prone position the patient employed the characteristic "leg-climbing" maneuver. A brace had to be worn because of the considerable weakness of the muscles of the back and advanced scoliosis. The patient's weight was 60 Kg.

CASE 6.—L. V., a 27 year old woman, entered the New York Hospital on April 30, 1934, complaining of generalized weakness and wasting of the muscles. Fourteen years before (1920), at the age of 13, she had had an attack of "influenza" which confined her to bed for three months. During convalescence she noted stiffness and progressive weakness of the right leg, which made ascending the stairs increasingly difficult. About a year later (1921) the left leg became similarly affected, and soon after she first experienced difficulty in getting up from a sitting position. The weakness gradually increased and extended to other muscle groups, especially those of the shoulders and back. The patient was able to perform her household duties until two years before admission to the hospital (at the age of 25, in 1932), when she fell and bruised her ankle and was confined to bed. The weakness increased rapidly, and the patient since has been unable to walk. The past personal history was otherwise irrelevant. The family history was noncontributory.

Examination revealed wasting of the shoulder muscles, with flaring of the scapulae and advanced symmetrical wasting of the lower extremities. Both feet were drawn into the equinovarus position. Practically all the skeletal muscles, except those of the face, were extremely weak. The tendon reflexes could not be elicited. There was no sensory disturbance. The patient's weight was 50.7 Kg.

61. In the neurologic service of Dr. Foster Kennedy, who has allowed us to publish the notes on these cases.

CASE 7.—A. S., a 29 year old woman, entered the New York Hospital on Oct. 15, 1935, complaining of weakness of the arms and legs of many years' duration. Since the age of 12 there had been progressive weakness of the legs. At that time she was unable to play as well as other children. Then she found it difficult to rise from the floor or from a sitting position, and she had to help herself up-stairs by pulling on the railing. When getting up from the floor she had to "climb up" on herself. The weakness increased slowly but steadily. Later the shoulders and upper parts of the arms were involved. Gradually the ability to walk became more restricted—she was able to walk slowly; then she walked only if some one assisted her to her feet and fell easily if the toes touched the edge of the carpet. For the past four years the patient had been bedridden and unable to lift the arms above the waist line. A sister who was similarly affected died at the age of 33 years.

Examination showed extreme muscular disability. The patient was unable to change her position in bed and could sit up only with support. The arms could not be lifted from the bed, but if the food was placed close to the mouth, she was able to feed herself slowly. There was considerable wasting of the muscles of the shoulders and upper parts of the arms. The calves were of normal size, but there was almost complete loss of muscular power. The deep tendon reflexes were absent. The patient weighed 54 Kg.

CASE 8.—H. R., an Austrian housewife aged 28, entered the New York Hospital in October 1932, complaining of weakness in the arms and legs. The complaint had its onset in July 1930. Since then, she had had increasing difficulty in ascending the stairs and in lifting objects. The weakness was progressive and at the time of admission was particularly notable when arising from a sitting to a standing position or when climbing stairs. At no time was there pain in the muscles. The past history was otherwise noncontributory. The family history was irrelevant except that one of the patient's five sisters had a similar syndrome.

Examination revealed generalized weakness of the muscles of the legs, particularly of the iliopsoas and extensor quardiceps groups, which was most marked on the right. The muscles were all large. There was atrophy of the erector spinae muscles. The supraspinatus and infraspinatus muscles were weak and of a wooden consistency. The muscles of the arms were reduced in power, but the size was not unusual. The tendon reflexes were not exceptional. There was no sensory defect. The patient weighed 59 Kg.

CASE 9.—H. L., a business man aged 44, entered the New York Hospital on Sept. 28, 1934, complaining of muscular weakness of seven years' duration. At the age of 36 he had first noticed weakness in the right foot and pain in the right great toe. The muscles of the right leg gradually became weak. The left leg remained practically unaffected for several years but then also gradually became weak. The shoulders subsequently became weak. The past and family histories were otherwise noncontributory.

Physical examination revealed that the patient walked with a limp and that the right foot was fatigued readily. He could raise his right arm only to a horizontal position. The left arm, however, could be raised over his head without difficulty. There were wasting and weakness of the deltoid, infraspinatus and supraspinatus muscles. The biceps muscles were weak. The left arm was slightly stronger than the right. The hand grip was good on both sides. The patient was able to rise from the prone to the erect position without supporting himself against his knees or thighs. The iliopsoas muscles were strong. The feet could be extended and flexed but were weak. The tendon reflexes were sluggish. The superficial abdominal reflexes were brisk. The patient weighed 60 Kg.

CASE 10.—M. S., an 18 year old girl, was admitted to the New York Hospital on Sept. 18, 1934, complaining of muscular weakness. The patient had been a professional dancer from the age of 4 years. About three and a half years before admission (1930) she observed that when doing the "split" she could not get up. Shortly after this she had to stop her stage performances, although she was still able to do complicated foot movements. Two years before admission (1932) these became impossible. She then began to have difficulty in climbing the stairs and even in stepping to the curbstone without support. She was obliged to use her arms to raise herself from a chair and to "climb up her legs" in rising from a recumbent position. The last had become impossible during the last two years, and the weakness grew gradually worse. No history of a similar disease existed in the family. The past history was otherwise noncontributory.

Physical examination revealed bilateral foot drop. The patient was unable to dorsiflex either foot. The left leg was weaker than the right, and the calf and thigh on the left were smaller in diameter than those on the right. Extension of the left leg at the knee was impossible. The patient walked with a waddling gait, with deviation to the left. She could stand erect only by putting her feet at right angles to each other. The knee and ankle jerks were not obtained, nor were the triceps or radial periosteal reflexes. There was no weakness of the arms, neck or trunk. The biceps jerk was present on both sides, and the abdominal reflexes were equal and briskly active on the two sides. There was no pseudohypertrophy. The patient weighed 51.2 Kg.

CASE 11.—C. M., aged 21, was admitted to the New York Hospital on Aug. 8, 1934, complaining of weakness of the extremities. In May 1931 she first became aware that she tired rapidly, particularly in the legs. She also became less steady in walking. At about the same time she noticed difficulty in extending her arms when flexed, as in opening an umbrella or handling a book. In September 1931 she became unable to raise herself from a chair. Her condition grew progressively worse until on admission to the hospital she could not elevate herself in bed or lift her head from the pillow. When eating she was obliged to prop her elbows on the table. She could walk when placed on her feet and given support. On Aug. 4, 1933, while attempting to board a street-car, she fell and fractured her skull. The past and family histories were otherwise noncontributory. There was no evidence of muscular dystrophy in any other member of the family.

Physical examination revealed marked generalized weakness. She was unable to abduct her arms, lift her head from the pillow, raise herself to a sitting or standing posture, lift her legs from the recumbent position or sit down unassisted from a standing position. There was advanced atrophy of the muscles of the shoulders and the upper and lower parts of the arms and the lower part of the left leg. The thighs were well developed, as were the gluteal muscles. Both calves were firm and of a wooden consistency. All other muscles were slack. There was definite scoliosis. The tendon reflexes were not elicited in either the upper or the lower extremities. The abdominal reflexes were absent. The face was not affected. The patient weighed 44 Kg.

CASE 12.—B. M., a newspaper man aged 25, entered the New York Hospital in September 1932, complaining of extreme weakness of the muscles of the shoulder girdle, upper parts of the arms, hips and thighs. At the age of 14 (1921) the patient first noticed difficulty in climbing stairs; he felt weak in the legs and had pain in the knees. Walking became more difficult and stepping up almost impossible. He had great difficulty in rising from a chair. After

sustained effort he had soreness in both knees and in the neck and lower part of the back. He fell readily, and in order to rise to the erect position he had to "climb up his legs." The weakness persisted and grew gradually worse until two years before (1930), when progress seemed to reach a standstill. The past personal history was otherwise irrelevant. The family history was not significant, except that the father was an extremely muscular man, who worked as a coal miner. One sister had had two "nervous breakdowns."

Examination revealed atrophy of the muscles of the arms and shoulders and, to a less extent, of the hands. The biceps, triceps, radial and periosteal reflexes were reduced or absent. The shoulder girdle was loose. There were weakness of the serratus anterior, rhomboideus, deltoid and pectoral muscles and atrophy and weakness of the latissimus dorsi muscle. Both sides seemed to be equally affected. There were, moreover, weakness of the erector spinae, abdominal and abductor and adductor muscles of the legs and weakness and atrophy of the extensor and flexor muscles of the thighs. The knee jerks were reduced or absent, although the ankle jerks were brisk. The calves were greatly hypertrophied. The gastrocnemius and soleus muscles were less weak than the other muscles of the leg. The extensor muscles of the feet were weak. The plantar responses were not unusual. There were no sensory changes. The patient weighed 57 Kg.

Case 13.—F. B., a pool-room keeper aged 28, entered the New York Hospital in 1932, complaining of generalized weakness, which had its onset in 1910. At this time, at the age of 6, he was weaker than other boys, in spite of the fact that he looked muscular. At the age of 14 (1918) he began to have difficulty in going up-stairs. At the age of 23 (1927) his legs became so weak that he could not walk and since that time had been more or less restricted to a chair. The muscles of the upper parts of the arms, the shoulders and the upper parts of the legs gradually wasted. His general growth was slower than the average, and his height was less than usual for boys of his age. He began shaving at the age of 18 (1922). The weakness and muscular wasting increased throughout his long incapacitation. At the time of admission to the hospital he could not lift his hands to his face and could stand erect only after being elevated to an erect position, and then only with extreme lordosis. The past history was otherwise of no importance. The family history was noncontributory, except that one brother possessed especially large muscles and had a local reputation as a fighter and wrestler.

Examination revealed muscular wasting, most marked in the biceps, triceps and forearm muscles. The deltoid and pectoral muscles were atrophic. The supraspinatus and infraspinatus muscle groups were weak and had a wooden consistency. The muscles of the thighs, legs and feet, more particularly the proximal than the distal, were wasted. The triceps and radial tendon reflexes were present, but the biceps reflex was absent. The abdominal reflexes were present. Knee and ankle jerks were absent, but the plantar responses were not unusual. The muscles of the head and neck were not weak. The patient weighed 49 Kg.

Case 14.—A. S., aged 22, was admitted to the Bellevue Hospital [61] on Aug. 14, 1933, complaining of muscular weakness. The onset of the present illness was insidious, beginning at the age of 11 (1922) with weakness of the legs. Fatigability was excessive, but after resting for a period, the child could go on with his play. He had no pain at any time. At the age of 13 (1924) he noticed difficulty in climbing stairs; he could lift one foot to the next step, but he could raise the weight of his body after it only with difficulty. At the age of 15 (1926) his gait was waddling, and he had difficulty in getting up from low chairs, from kneeling

and from a recumbent position. At about the same time his hand grasp became less strong. At the age of 16 (1927) he noted difficulty in standing on the right foot because the extended leg gave way at the knee. Atrophy of the legs followed. Although his hands gradually became weaker, he noticed no loss of tissue. They failed, however, to increase in size after his eleventh year. During the year preceding his admission he had felt at intervals a warm, burning sensation on the face, neck, arms and back. At the time of admission he could sit up but could not walk. Symptoms of sphincter disturbance had never been present. The past history was otherwise noncontributory. Two brothers had similar muscular defects.

Physical examination revealed no weakness of the muscles of the larynx, pharynx or jaws, but there was generalized malnutrition with atrophy of the trapezius and sternocleidomastoid muscles. Moreover, there were marked lordosis and advanced wasting of the muscles of the extremities. The patient could not rise from bed unaided and moved his arms and legs feebly. Although the muscular wasting and slackness were extreme, no fibrillations were noted. The feet were in the equinovarus position, with dorsiflexion of the toes. When the legs were moved, contraction of the proximal part of the peroneal group of muscles could be seen, but there was little to be noted in the atrophied distal parts. All tendon reflexes were absent. The muscles of the neck and shoulders were particularly weak, and there was unnatural mobility of the shoulder joints. The patient weighed 49.5 Kg.

CASE 15.—E. R., an 11 year old girl, entered the New York Hospital on June 22, 1934, complaining of difficulty in walking. She had appeared normal until the age of 7 (1930), when her difficulty in walking began. Then the ability to walk up-stairs was lost, and she was unable to rise unaided from a recumbent position. The past history was otherwise noncontributory. A 16 year old sister was similarly affected.

On examination the patient revealed considerable weakness and wasting of the muscles of the shoulders, back and lower extremities. The scapulae appeared to be loosely attached, and there was moderate "winging." The arms could be raised above the head with great difficulty. The patient walked with a waddling gait and with lordosis. The peroneal muscles were weak, but the calves were large and of wooden consistency. Both feet were drawn into an equinovarus position. The tendon reflexes of the legs could not be elicited. The patient weighed 31.9 Kg.

CASE 16.—C. R., a sister of E. R. (case 15), was first examined in October 1934, at the age of 15 years. She had been totally incapacitated for about two years. Until the age of 7 (1926) she had been able to play and run about with the same facility as that of her playmates. She then began to notice weakness in running and walking, which progressed gradually and limited her activities more and more. At about the age of 10 (1929) she had difficulty in raising her arms, which, like the disability in walking, progressed gradually. At the age of 13 (1932) the patient was totally incapacitated. She was unable to walk, stand or raise her arms. Since then she has been confined to bed. There was wasting of the muscles of the shoulder girdle and the proximal muscles of both the upper and the lower extremities. The patient weighed 45.5 Kg.

CASE 17.—W. K., a 17 year old boy, entered the New York Hospital in June 1934, complaining of difficulty in walking of three years' duration. In 1931 he first noticed difficulty in ascending stairs and began to rely on the assistance afforded by his hands and arms. He insisted that weakness in the legs was of sudden onset and was accompanied by a cramped feeling and sharp, steady pains in the calves

and lower portion of the thighs. Thereafter weakness was progressive. He complained of pain in and about the joints from time to time. Walking became more difficult and was possible only with the assumption of a lordotic position and swinging the hips. He fell to the floor repeatedly because of sudden collapse of the legs at the knees, from which position he rose to the erect posture by "climbing up his legs." The past history was of no interest except that he had had a convulsion two years before (1932). While he was stooping to pick up an object from the floor, his right hand became numb and began to shake, and shortly after he fell to the floor, apparently not aware of what was going on about him. He did not bite his tongue or urinate. The family history was of no interest except that one sister had "rheumatism in her legs."

Examination revealed slight wasting of the deltoid muscles and the muscles of the shoulder girdle. There were winging of the scapulae and marked atrophy and weakness of both biceps muscles. The grip was fairly strong. The muscles of the calves showed pseudohypertrophy, but there were wasting of the hamstring muscles and weakness of the extensor quadriceps group. The erector spinae muscles were weak and atrophied. The patient weighed 61 Kg.

CASE 18.—A. R., a 10 year old boy, entered the New York Hospital on Jan. 23, 1936. It was noticed that at the age of 3 years he walked with an arched back and protuberant abdomen and that he had a tendency to "climb up" on himself when rising from the floor or chair. The difficulty in walking progressed gradually. At the age of 9 years he was unable to get up from a chair unaided. A few years after onset of the difficulty in walking, the arms became involved. The muscular disability progressed slowly until, at the time of writing, he was unable to get up alone, stand or walk. The arms can still be lifted as high as the shoulders with the use of accessory muscles. The past personal and family histories are noncontributory. Examination showed considerable wasting and weakness of the muscles of the shoulder girdle and upper parts of the arms. There was prominent flaring of the scapulae. The calves were large but of wooden consistency, and the muscles were weak. There was considerable foot drop on both sides. The tendon reflexes were much diminished. The patient weighed 35 Kg.

CASE 19.—A. F., a man aged 55, an Italian, entered the New York Hospital on May 22, 1935, complaining of progressive difficulty in walking for the past two years. The onset was gradual. A son (case 20) was similarly afflicted.

Examination showed moderate weakness of the muscles of both legs. The muscles of the thighs were wasted, and both calves were abnormally large and of wooden consistency. There was slight weakness of the arm muscles. The triceps muscles on both sides showed wasting. The patient was unable to rise from a sitting position without difficulty, and on getting up from the prone position he "climbed up on himself." The knee jerks were absent, and the triceps reflexes were weak. The biceps, abdominal and cremasteric reflexes and ankle jerks were normal. The patient weighed 70 Kg.

CASE 20.—V. F., a 25 year old man, a son of A. F. (case 19), entered the New York Hospital on May 22, 1935, complaining of weakness of the legs since the age of 15 years and of the arms for the past five years. The weakness progressed gradually until there were definite difficulty in walking and moderate difficulty in raising the arms above the head.

Examination showed weakness and wasting of the muscles of the thighs, shoulder girdle and upper part of the arms. The muscles of the calves were enlarged and weak. The knee jerks were absent, and the biceps and triceps reflexes were diminished. The patient weighed 65 Kg.

# ENCEPHALOMYELITIS COMPLICATING MEASLES

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An increasing number of cases of encephalitis following measles have been reported in the literature in recent years. The majority of these have been of early acute forms, the only instance of a late form being the case described by Walthard.[1] The comparative rarity of the disorder and its still disputed etiology and pathogenesis justify further investigation. The present contribution is based on an analysis of one case of an early and one of a late stage of this disease, making a comparative study possible.

## REPORT OF CASES

Lab # 3671

CASE 1.—*Clinical History.*—E. G., a boy aged 6 years, had generalized clonic convulsions and became comatose three days after the appearance of a typical measles rash.

Physical Examination: The temperature was 110 F.; the skin was dry and hot, and there was a generalized morbilliform eruption. The rate of respiration was 50 per minute; breathing was shallow and labored, and rhonchi were heard throughout the chest. The pulse could not be felt; the heart action was rapid and irregular, but there were no murmurs. The abdomen was firm.

Neurologic Examination: The head was retracted and the neck rigid; the pupils were dilated, and there was deviation of the eyes to the right, accompanied by nystagmoid jerks. There were constant twitchings of the right side of the face and intense clonic convulsions of the body, more pronounced on the right.

Examination of the blood showed 12,600 white cells per cubic millimeter and a hemoglobin concentration of 96 per cent. The Kahn test of the blood gave a negative reaction. Examination of the urine showed nothing abnormal. The spinal fluid was under increased pressure; it was turbid and contained a trace of globulin and an occasional leukocyte.

After the administration of sodium amytal, the convulsions ceased, but signs of bronchopneumonia and respiration of the Cheyne-Stokes type developed; the patient died twelve and one-half hours after admission to the hospital.

*Gross Postmortem Examination.*—There was bronchopneumonia, but no other significant change in the internal organs. The weight of the brain was 1,340 Gm. The leptomeninges were markedly congested and edematous, and the basal vessels were delicate. In frontal sections the cortex was of normal width, hyperemic and poorly demarcated from the white matter. The latter was edematous, and its blood vessels were injected. There was also hyperemia in the basal ganglia,

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From the State Psychopathic Hospital, the University of Michigan.

1. Walthard, K. M.: Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:176, 1930.

brain stem and cerebellum. The ventricles were of normal width, and the ependyma was smooth. The spinal cord was not available.

*Histologic Examination.*—The pia-arachnoid contained patchy accumulations of polyblasts (large and small mononuclear forms) and microglia cells. There were moderate numbers of lymphocytes and plasma cells in the perivascular spaces. The blood vessels were distended and congested, but there were no thrombi or hemorrhages.

In the brain the most striking changes were countless perivascular lesions, disseminated throughout and presenting a uniform picture. They were not sharply circumscribed but merged indefinitely with the surrounding tissue. In Nissl

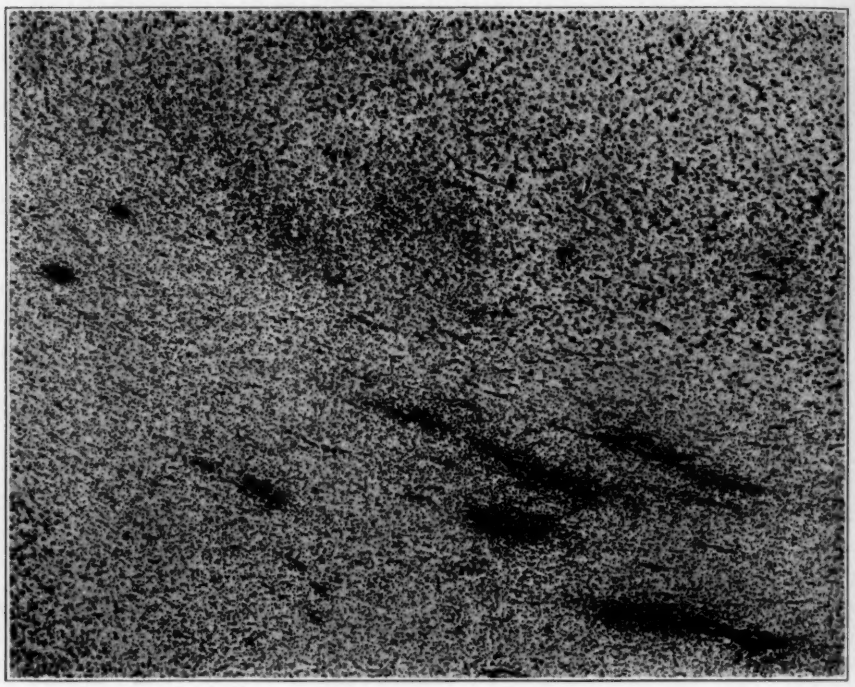

Fig. 1 (case 1).—Perivenous distribution of the lesions, occurring in the border zones of the gray and white matter of the cerebrum. The lesions in the cortex are diffuse, and are more discrete in the white matter. Nissl stain, Zeiss planar lens, 35 mm.

preparations (fig. 1) these foci consisted of a cellular syncytium forming a sheath which occurred almost exclusively about the small veins (as demonstrated with Weigert's elastica and Van Gieson's connective tissue stains). The cells were composed largely of polyblastic glial cells (fig. 2), which could be subdivided into: (1) microglia cells, (2) large gitter cells with small, dark nuclei and irregular cell bodies and (3) small mononuclear forms (Wickman's "polyblasts"). The microglia cells were numerous in Hortega's silver carbonate preparations. With the scarlet red stain the gitter cells were empty for the most part, disclosing only scant deposits of fat in the form of occasional fine droplets. Lymphocytes and

plasma cells were common in the distended perivascular spaces, occasionally invading the nerve tissue. There were no polymorphonuclear leukocytes. In Weigert sections (fig. 3) there were corresponding small perivascular areas of demyelinization, with few fragmented myelin sheaths and balls in the faintly stained cellular syncytium. The axis-cylinders were severely involved and showed no evidence of relative preservation. There was no macroglia response and no fibrous glia in Holzer sections. Iron was not present in the lesions. There were no changes in the walls of the blood vessels, except for moderate swelling of the endothelium. There were occasional deposits of fat in adventitial cells both inside and outside the lesions.

Fig. 2 (case 1).—Higher magnification of a perivascular lesion, showing a layer of lymphocytes and plasma cells surrounded by a glial syncytium. Nissl stain; Zeiss objective, 16 mm.; ocular no. 2.

Cortex: There were numerous lesions in the cortex, which preferred the lower layers and the border zone between the gray and the white matter (fig. 1). As a rule they were direct extensions from foci in the white matter, but occasionally isolated lesions were observed in the upper layers of the cortex. All the cortical lesions were characteristically diffuse. The nerve cells within the lesions were not appreciably reduced, but revealed Nissl's "acute swelling" and "severe degeneration." The cyto-architecture of the cortex was well preserved, but the same parenchymatous changes occurred diffusely throughout the gray matter. The microglia and macroglia were diffusely proliferated, especially in parts of the first layer adjacent to the meningeal infiltration. All areas of the hemispheres, except for the cornu ammonis, were equally affected.

White Matter: In the white matter of both hemispheres the lesions were much more abundant than in the gray matter. Here they assumed the typical elongated perivenous form, occurring in groups rather than in isolated patches. All areas of the white matter were severely involved, but there were two sites of predilection: (1) in close proximity to the gray matter (as previously mentioned) and (2) in the neighborhood of the ventricles. Beneath the ependyma there was a well defined broad zone of polyblastic glia cells, in addition to the patchy perivascular lesions. The ependymal lining remained intact. There were no changes in the choroid plexus.

Basal Ganglia: The most severe involvement was present in the capsula interna, the capsula externa, the capsula extrema and the claustrum. In the

Fig. 3 (case 1).—Multiple areas of demyelinization surrounding the small medullary veins in the white matter of the cerebral hemispheres. Weigert-Kulschitzky stain; Zeiss planar lens, 75 mm.

putamen and the caudate nucleus there were scattered foci. In the pallidum only the part adjacent to the capsula interna was involved. The thalamus and hypothalamus were involved in the neighbohood of the third ventricle. The amygdaloid nucleus was affected only in its periphery. In the substantia innominata there were numerous lesions which appeared to be continuous with an intense subpial proliferation of glia in its vicinity. The involvement of the optic chiasm, the tuber cinereum and the corpora mamillaria was moderate. In all these regions, although both the gray and the white matter were involved, the lesions preferred the white substance of the capsules, the border zones of the gray substance and the subependymal areas.

Brain Stem: In the midbrain the most pronounced changes were present in the substantia nigra (fig. 4) and in the adjacent parts of the nucleus ruber. In the pons there were pronounced symmetrical involvement of the sensory nucleus of the fifth nerve and the middle cerebellar peduncle and moderate involvement of the pontile nuclei. In the medulla there were symmetrical lesions in the substantia gelatinosa and the ascending root of the fifth nerve; in the other cranial nuclei and in the pyramids the involvement was moderate. The olives were spared. In addition, throughout the brain stem there was a distinct marginal (subpial) proliferation of glia, identical with the subependymal involvement of the hemispheres. The perivascular changes in the deeper tissues appeared to be an extension of this marginal involvement. In general, although the border zones of the gray

Fig. 4 (case 1).—Numerous lesions in the substantia nigra and the adjacent parts of the nucleus ruber (in the upper part of the picture). Nissl stain; Zeiss planar lens, 20 mm.

and white matter were preferred, there was relatively greater involvement of the gray matter in the brain stem than in the cerebral hemispheres.

Cerebellum: There were few perivascular lesions in the white matter of the cerebellum. The gray matter and the dentate nucleus were spared.

The diffuse parenchymatous changes and glial proliferation observed in the cortex were also present in the basal ganglia and the brain stem.

This case was clinically and patho-anatomically a typical example of the early acute phase of postmeasles encephalitis. The spread of the lesions followed three main modes of distribution: (1) perivascular

(perivenous), (2) subependymal and (3) marginal. The perivascular lesions were, as a rule, encountered in the white matter, from which they appeared to extend into the gray matter, thus preferring the border zones of the gray and white matter in the cortex and the basal ganglia. The subependymal distribution could likewise be followed in the diffuse involvement of the periventricular tissues in the hemispheres and the basal ganglia. Finally, a marginal distribution was encountered in the brain stem. From the subependymal and subpial lesions extensions into the neighboring gray matter occurred as in the cortex. Histologic analysis of the lesions disclosed definite degenerative, proliferative and exudative phenomena. Degenerative changes occurred in the form of perivascular demyelinization and corresponding involvement of the axis-cylinders. Proliferative changes consisted of a perivascular syncytium of microglia cells, polyblasts and gitter cells, without evidence of fat Abbau in the gitter cells. Exudative phenomena were characterized by accumulations of lymphocytes and plasma cells in the perivascular spaces.

Lab #3679

Case 2.—*Clinical History.*—W. McV., a boy aged 8 years, was brought to the hospital six days after the appearance of a measles rash. Instead of the usual drop, his temperature had remained elevated. He became listless and at the time of his admission had lapsed into deep stupor.

Physical Examination: The child was acutely ill, irritable and confused, and became comatose when left alone. A typical morbilliform eruption was present. A systolic murmur was heard over the apex of the heart. The bladder reached half-way to the umbilicus.

Neurologic Examination: The pupils were constricted and reacted poorly to light. There were ptosis of the right eyelid and lateral deviation of the right eye. The patient assumed a position of opisthotonos, but there was no definite stiffness of the neck. Kernig and Brudzinski signs were not present. There was generalized hypertonicity; all the deep tendon reflexes were hyperactive. Abortive patellar and ankle clonus and a questionable Babinski sign were elicited. The abdominal and cremasteric reflexes were absent.

Examination of the urine showed nothing abnormal. Examination of the blood revealed 4,100,000 red cells and 6,100 white cells per cubic millimeter, of which 45 per cent were polymorphonuclears and 53 per cent lymphocytes. The hemoglobin concentration was 78 per cent. The Kahn reaction of the blood was negative; there was 86 mg. of sugar per hundred cubic centimeters of blood. Repeated spinal punctures showed a clear fluid, under low pressure; the cells were not increased, and the sugar content was about 60 mg. per hundred cubic centimeters of fluid.

*Course.*—The child became progressively worse and remained in deep coma. Three weeks after the onset of measles the temperature rose to 107 F., and the patient died.

*Gross Postmortem Examination.*—There was terminal bronchopneumonia, but otherwise no significant changes. The brain weighed 1,390 Gm. The leptomeninges were congested and edematous, and the basal vessels were delicate. In frontal sections the cortex was of normal width, moderately hyperemic and well demarcated from the edematous white matter. In the latter the blood vessels were

injected and surrounded by indistinct narrow, grayish red zones. The ventricles were of normal width, and the ependyma was smooth. The basal ganglia, cerebellum, brain stem and spinal cord were likewise hyperemic, but there were otherwise no gross changes.

*Histologic Examination.*—The pia-arachnoid was thickened and contained in its meshes numerous fibroblasts, a few polyblasts and an occasional lymphocyte and plasma cell.

In the brain the most impressive changes were countless perivascular lesions, almost entirely limited to the white matter. In Weigert sections (fig. 5) elongated patches of demyelinization of varying width, surrounding the medullary veins, gave the white substance a moth-eaten appearance. The lesions were poorly circum-

Fig. 5 (case 2).—Numerous partly coalescing foci of demyelinization in the white matter of the cerebral hemispheres. Weigert-Kulschitzky stain; Zeiss planar lens, 75 mm.

scribed, merging with normal tissue and displaying a tendency to coalesce. These changes were present in the centrum semiovale, corona radiata, corpus callosum, capsula interna, capsula externa and capsula extrema. In the cortex and the gray matter of the basal ganglia, brain stem and spinal cord, there were few demyelinated foci. There was also rarefaction in the subependymal white matter. Distinct marginal demyelinization was present in the pons, medulla and cord. As a rule the demyelinization was not complete, the myelin sheaths showing rarefaction, thickening, fragmentation and beading. Enclosed in the lesions of the myelin sheaths were numerous round gitter cells, which as a rule extended beyond the zone of demyelinization. The axis-cylinders in the lesions showed corresponding intensity of involvement, with no evidence of relative preservation.

In Nissl preparations (fig. 6) the lesions appeared as diffuse coalescing foci containing large numbers of gitter cells, few microglia cells and very few lymphocytes and plasma cells, in both the perivascular spaces and the surrounding tissue. The most instructive picture was obtained with the scarlet red stain (fig. 7), which showed gitter cells laden with coarse fat drops forming broad, poorly delimited perivascular zones and infiltrating the perivascular spaces. In the periphery of the lesions there were fairly numerous protoplasmic and few fiber-forming astrocytes. Iron was not present. The endothelium of the distended blood vessels was moderately swollen, but there were no thrombi or hemorrhages.

The scattered lesions in the cortex contained fat-laden microglia cells localized along the course of the demyelinated radial fibers, but there were few gitter cells. The cyto-architecture of the cortex was well preserved, but the nerve cells showed

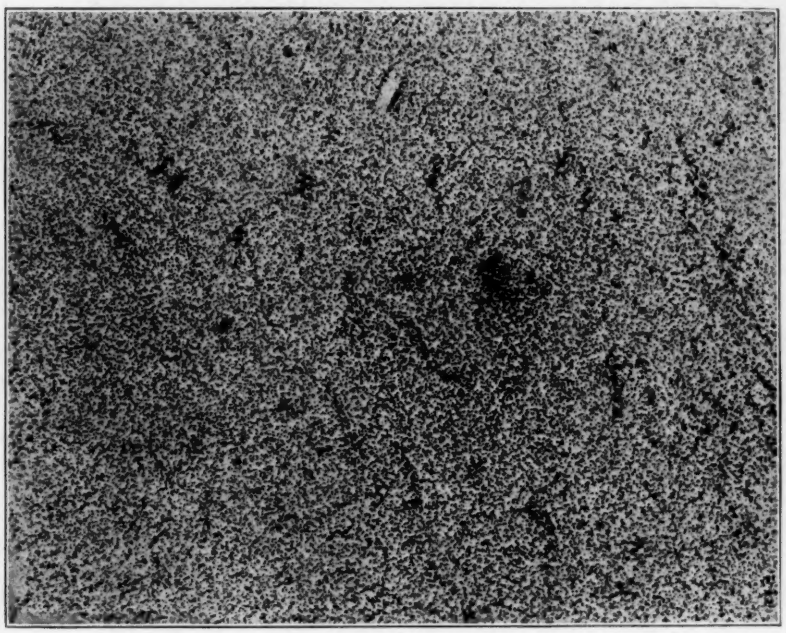

Fig. 6 (case 2).—Characteristic diffuse glial proliferation within the lesions in the white matter, which is mostly composed of gitter cells. Nissl stain; Zeiss planar lens, 35 mm.

far advanced, acute, severe and ischemic degeneration, which appeared most pronounced in the third layer. There was also diffuse proliferation of fat-laden microglia and macroglia cells. This was most pronounced in the first layer. These diffuse changes were also present in the gray matter of the basal ganglia, brain stem and spinal cord.

Distribution of the Lesions (Nissl): Cerebral hemispheres: The entire white matter, including the corpus callosum, was equally and severely affected, the lesions being almost exclusively perivenous. There was also an outspoken diffuse subependymal proliferation (fig. 8), especially about the posterior horns of the ventricles, which severely affected the Gratiolet fibers and the adjoining splenium

of the corpus callosum. The ependyma and the choroid plexus were not changed. In the cortex there were a few scattered lesions, extending as a rule from the white matter and affecting the lower layers.

Basal Ganglia: There were numerous foci in the capsula interna, the capsula externa and the capsula extrema. These extended into the claustrum and the adjacent peripheral zones of the striate bodies. The thalamus and globus pallidus were spared, but the adjacent parts of the optic tracts were severely involved.

Brain Stem: The midbrain was almost entirely spared, only a few scattered lesions appearing in the white matter. In the pons the most significant change was a diffuse marginal glial proliferation (fig. 9), most pronounced in the lateral and ventral parts, frequently extending into the fibers of the pyramidal tracts

Fig. 7 (case 2).—Fat-laden gitter cells are seen in the perivascular space and surrounding tissue. Scarlet red stain; Zeiss objective, 16 mm.; ocular no. 2.

but avoiding the pontile nuclei. In the medulla a similar marginal proliferation extended from the surface into the white matter surrounding the substantia gelatinosa and the nucleus cuneatus.

Cerebellum: A few foci were observed in the white matter of the cerebellum, but the gray matter and dentate nucleus were spared.

Spinal Cord: There was severe marginal involvement of the lateral and ventral parts of the cord, extending chiefly into the lateral and ventral pyramidal tracts.

This case, in which the duration of illness was about three weeks, presented the patho-anatomic characteristics of a late form of measles encephalitis. The progression of the lesions to broad, coalescing patches of demyelinization with signs of pure Abbau and beginning

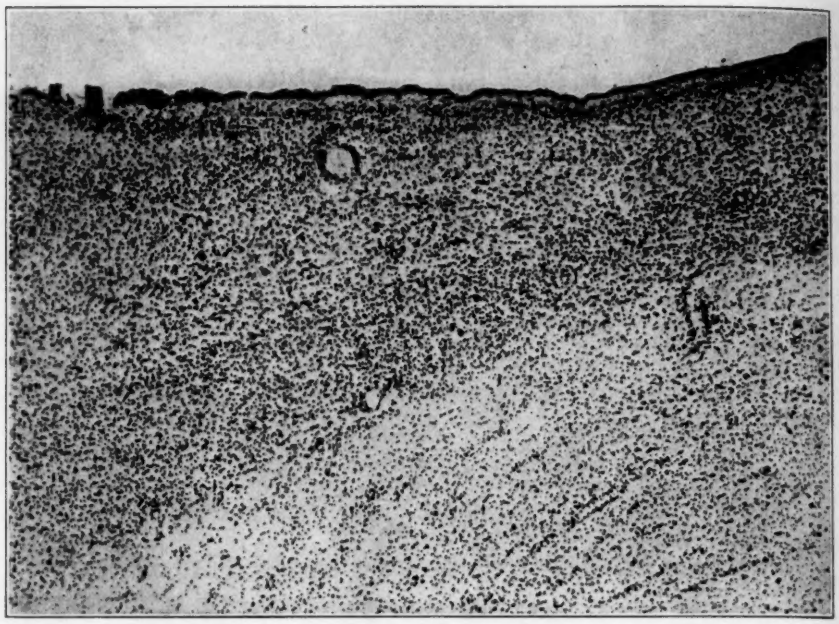

Fig. 8 (case 2).—Subependymal distribution, with a broad zone of glial proliferation can be seen in the vicinity of the posterior horn of the lateral ventricle. The ependyma is intact. Nissl stain; Zeiss planar lens, 20 mm.

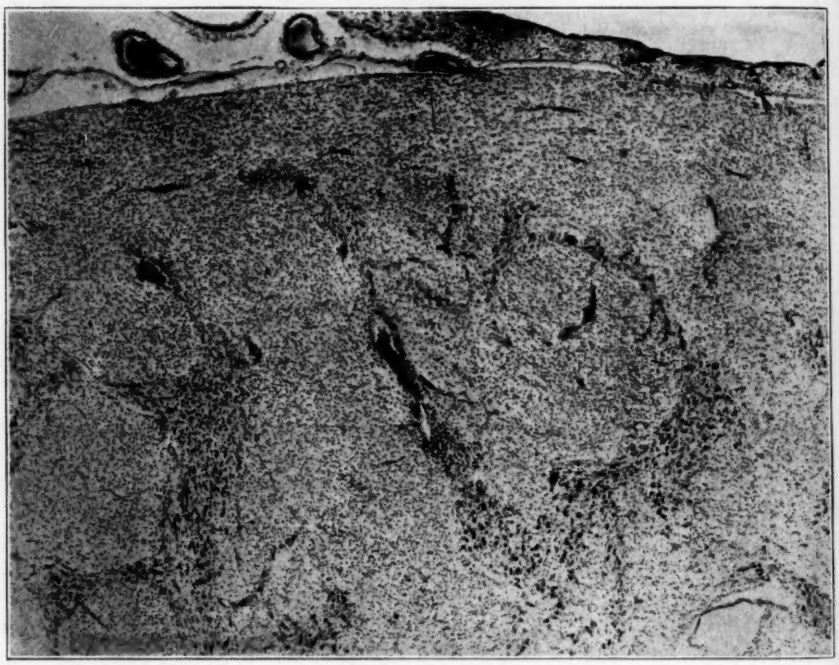

Fig. 9 (case 2).—Marginal distribution, showing the diffuse glial proliferation extending from the surface into the white matter, and sparing the gray matter of the pons. Meningitis is apparent. Nissl stain, Zeiss planar lens, 35 mm.

organization, indicated an end-stage of the process. Exudation of hematogenous elements and proliferation of microglia were no longer present, having been replaced by gitter cells engorged with fat and beginning repair by the macroglia. A large part of the myelin sheaths in the lesions and a proportionate number of the axis-cylinders were destroyed. The predilection of the lesions for the white matter and the perivascular (perivenous), subependymal and marginal modes of distribution were very distinct here.

## GENERAL COMMENT

The clinical manifestations of acute disseminated encephalomyelitis complicating measles are well known and are uniform in all cases reported, making clinical discussion of little value. This presentation, therefore, will be devoted entirely to an analysis of the patho-anatomic changes.

The anatomic picture of this form of encephalitis is that of a disseminated perivascular (perivenous) focal disturbance belonging to type 6 of Spatz.[2] This type is restricted to a small group, being encountered only in measles, after vaccination and in a few conditions of unknown etiology. A precise description of the distribution of the lesions has been offered by Wohlwill,[3] who distinguished three predominant types: (1) marginal (subpial), (2) subependymal and (3) perivascular (perivenous), the first occurring in the spinal cord, the second in the vicinity of the ventricles and the third chiefly in the white substance of the hemispheres. These observations were confirmed in both cases reported here, the only difference being the unusually severe changes in the gray matter in case 1. The involvement of the gray matter in this case, however, was merely an extension from the three principal areas just mentioned, since it occurred mainly in the border zones of the gray and white matter and in the gray masses in the vicinity of the ependyma and meninges. This is also in agreement with the observations of Wohlwill,[3] who attributed the characteristic modes of distribution to the perivenous spread of the lesions. Thus, in the cord the marginal involvement corresponds closely to the area drained by the vasocorona. The involvement in the hemispheres follows the course of the medullary veins. Finally, through communications between the adventitial and the subarachnoid spaces, the involvement of the periventricular tissues takes place.

Histologically, the most significant changes observed in the lesions are perivascular demyelinization, glial proliferation and, less frequently, signs of infiltration, congestion and hemorrhage. The relative frequency

2. Spatz, H.: Encephalitis, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 2, pt. 7.

3. Wohlwill, F.: Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:20, 1928.

of and emphasis placed on one or another of these changes have led to different interpretations of the nature of the disorder. Two main opposing views have been advanced. The one stresses the "toxic" and degenerative character of the process (Bergenfeldt,[4] Brock,[5] Mosse,[6] Zimmerman and Yannet [7] and Ferraro and Scheffer [8]), and the other, its inflammatory nature (Reimold,[9] Greenfield [10] and others). A number of investigators have expressed doubt of the possibility of defining the nature of the process from purely morphologic data (Spielmeyer,[11] Wohlwill [3] and Walthard [1]). At the outset it must be stated that the entire picture, not merely one or another of its components, should form the basis for interpretation, and that it is necessary to guide oneself by an adequate definition of encephalitis. According to modern views (Spatz [2]), encephalitis is the independent occurrence of an inflammatory reaction on the part of the vascular connective tissue apparatus, characterized by cellular infiltration and active transformation of the glia, directed against a virus. In line with Hortega's views, the microglia cells and their variants (Maximow's polyblasts) are the reacting elements. That one or the other of these various components of an inflammatory reaction can assume a predominant, and even exclusive, rôle is being more and more recognized, through the study of the various encephalitides. Spielmeyer [11] thus expressed the opinion that the almost purely glial character of the lesions in measles encephalitis does not necessarily argue against its inflammatory nature.

The assumption of a degenerative process is based on the rarity of infiltration phenomena, the emphasis of demyelinization in the lesions and the consideration that the glia functions only in Abbau and repair. Such contentions are not borne out by a closer analysis of the cases reported in the literature and in this paper. The varying reports and interpretations of other authors are based exclusively on observations of early or late stages of the disease and not on comparative studies. In the majority of cases of the acute stage, inflammatory phenomena (exudation of cells and microglia cells) were common (Reimold,[9]

4. Bergenfeldt, E.: Acta med. Scandinav. **61**:281 1924.

5. Brock, J.: Ztschr. f. Kinderh. **40**:552, 1926.

6. Mosse, K.: Jahrb. f. Kinderh. **112**:272, 1926.

7. Zimmerman, H. M., and Yannet, H.: Encephalomyelitis Complicating Measles: Report of Case with Necropsy, Arch. Neurol. & Psychiat. **24**:1000 (Nov.) 1930.

8. Ferraro, A., and Scheffer, I. H.: Encephalitis and Encephalomyelitis in Measles: Pathologic Report of Six Cases, Arch. Neurol. & Psychiat. **25**:748 (April) 1931.

9. Reimold, W.: Monatschr. f. Kinderh. **37**:336, 1927.

10. Greenfield, J. G.: Brain **52**:171, 1929.

11. Spielmeyer, W.: Monatschr. f. Kinderh. **44**:195, 1929; Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:161, 1930.

Wohlwill,[3] Musser and Hauser,[12] Greenfield,[10] Ferraro and Scheffer [8] and Peterman and Fox [13]). In conditions of longer duration, degenerative signs (fat Abbau) were predominant, giving the impression of a purely degenerative disorder (Brock,[5] Mosse [6] and Walthard [1]). The cases reported here make a comparative study possible. Case 1 illustrates the early stages of the inflammation, the lesions being frequently infiltrated with lymphocytes and plasma cells. The glia formed a perivascular syncytium composed purely of microglia cells and polyblasts, which obviously are mesodermal derivatives. The gitter cells were transformed microglia cells, with empty gitter structure and no fat content. Such cells were evidently not playing the rôle of Abbau of degenerative products but appeared to be a direct reaction to the noxious agent. Moreover, the proliferation of the glia was proportionately greater than the accompanying demyelinization. The contention that demyelinization per se excludes inflammation is not borne out by facts. Although comparatively rare, it may be observed in inflammatory conditions caused either by bacteria or by a filtrable virus. I have observed a striking similarity to the demyelinization of measles encephalitis in a case of metastatic encephalitis complicating endocarditis due to Streptococcus viridans, in which mixed purulent and nonpurulent perivascular foci were equally demyelinated. In inflammatory conditions the demyelinization is merely an expression of the degenerative component of the inflammation. It may be that in measles encephalomyelitis involvement of the myelin sheaths is related to a specific action of the etiologic agent. In case 1, therefore, all criteria of inflammation, with its exudative, proliferative and degenerative properties, are fulfilled. In case 2 is shown the logical outcome of this antecedent process, representing its end-stage. Here all signs of inflammation had disappeared. The exudation of cells and the polyblastic activity were no longer in evidence. Instead, pure fat *Abbau, Abräumung* and beginning repair by the neuroglia had taken its place. The demyelinization, accordingly, had assumed greater prominence. It is therefore impossible from this stage alone to draw any conclusions about the nature of the condition, except when it is compared with the initial acute phases.

The prominence of the demyelinization, especially in the subacute phase of the disorder, has led some authors (Pette [14] and Putnam [15])

12. Musser, J. H., and Hauser, G. H.: Encephalitis as Complication of Measles, J. A. M. A. **90**:1267 (April 21) 1928.

13. Peterman, M. G., and Fox, M. J.: Encephalitis as Complication of Measles: Report of Thirteen Cases, Am. J. Dis. Child. **46**:512 (Sept.) 1933.

14. Pette, H.: Deutsche Ztschr. f. Nervenh. **105**:76, 1928; München. med. Wchnschr. **76**:225 (Feb. 8) 1929.

15. Putnam, T. J.: Studies in Multiple Sclerosis: Similarities Between Some Forms of "Encephalomyelitis" and Multiple Sclerosis, Arch. Neurol. & Psychiat. **35**:1289 (June) 1936.

to draw analogies with multiple sclerosis. These views have been based on supposed similarities in the two conditions. Actually, the differences are more striking than the similarities, as has been outlined in detail by Spielmeyer [11] and others. Thus, measles encephalitis is characterized by a specific type of distribution, exclusively perivenous and frequently affecting the gray as well as the white matter. Such changes are not characteristic of multiple sclerosis, in which the perivascular relationship of the lesions is often absent. Moreover, the indefinite outlines of the lesions in measles encephalitis, with their equal involvement of myelin sheaths and axis-cylinders, and the inflammatory nature of the glial reaction, contrast sharply with the circumscribed plaques of multiple sclerosis, with their affinity for myelin sheaths and early pronounced gliosis of a reparative nature. These fundamental differences are even more clearly revealed in comparisons of the acute stages of the two conditions. Acute multiple sclerosis is histologically identical with the usual type of that disorder. In an acute form of six weeks' duration observed in this laboratory, the typical plaques with their pronounced gliosis and demyelinization had already developed, indicating a process entirely different from the inflammation of measles encephalitis.

Various theories about the etiology of this disease have been advanced. Thus, the encephalitis has been attributed in turn to the virus of measles, to another unknown virus activated by the measles infection and to an anaphylactic reaction (Glanzmann [16]). The two views last mentioned are purely speculative. The clinical course, the frequent pleocytosis in the spinal fluid (Ford [17]) and the anatomic observations prove that this is an acute inflammatory disease of the brain, a true encephalitis produced by the virus of measles.[18]

SUMMARY

1. Two cases of encephalomyelitis complicating measles are reported, illustrating, respectively, the acute phase and the end-stage of the disorder.

2. The condition is interpreted as a true encephalitis.

3. The fundamental differences between measles encephalitis and multiple sclerosis are discussed.

16. Glanzmann, E.: Schweiz. med. Wchnschr. **57**:145 (Feb. 12) 1927.

17. Ford, F. R.: Bull. Johns Hopkins Hosp. **43**:140, 1928.

18. Since this paper was written, K. M. Walthard has reported similar observations and a similar interpretation of the condition (Ztschr. f. d. ges. Neurol. u. Psychiat. **157**:100 [Jan. 12] 1937).

# Case Reports

## A FORM OF CHRONIC EPIDEMIC ENCEPHALITIS SIMULATING THE LANDOUZY-DEJERINE TYPE OF PROGRESSIVE MUSCULAR DYSTROPHY

### Value of Studies on Creatine in Conjunction with Ingestion of Amino-Acid as an Aid in Differential Diagnosis

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So protean are the manifestations of chronic epidemic encephalitis, that one's diagnostic acumen is frequently taxed to the utmost in attempting to determine the exact nature of the syndrome that presents itself. This is especially true in the not uncommon cases in which the encephalitic onset is obscure or so transitory as to have been overlooked altogether. Then again, it is possible that the disease has become distorted since the severe pandemics of 1917 to 1920. Grinker [1] expressed the belief that it may not have an acute or subacute onset, the virus being so attenuated or the host so resistant that the disease process may be chronic from the beginning and run a progressive, slow, malignant course.

The most frequent localization of the lesions of epidemic encephalitis is in the extrapyramidal motor system, and all are familiar with the striopallidal syndrome resembling paralysis agitans, which this produces. However, many less common neurologic complexes may be produced, depending on the distribution of the lesions, for the disease has been found to be capable of involving almost every structure of the central and peripheral nervous system, in either an irritative or a paralytic disturbance. Of especial interest in this connection are the syndromes that resemble the primary muscular atrophies and dystrophies. Thus, Wimmer [2] reported two cases in which there were perivascular infiltration with lymphocytes and plasma cells in the lateral columns and atrophy of the motor cells of the anterior horns. These cases presented the syndrome of amyotrophic lateral sclerosis. Ornsteen [3] and others have reported similar cases. Froment and Gennevois [2] described a case of encephalitis exhibiting the Aran-Duchenne type of atrophy. Even the syndrome of myasthenia gravis has been observed—milder in degree than that of the idiopathic type and with a better prognosis.[2]

Given, then, a suspicious atypical neurologic complex, such as those mentioned, how is one to determine whether one is dealing with a chronic encephalitic process or with one of the large group of

From the Taunton State Hospital.

1. Grinker, R. R.: Epidemic Encephalitis, in Neurology, Springfield, Ill., Charles C. Thomas, Publisher, 1934.

2. Stewart, W. B.: Epidemic Encephalitis, in Piersol, G. A.: Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, 1932, vol. 5, pp. 105-120.

3. Ornsteen, A. M.: Syndrome of Amyotrophic Lateral Sclerosis in Epidemic Encephalitis, J. Nerv. & Ment. Dis. **72**:369 (Oct.) 1930.

primary muscular atrophies and dystrophies? This important problem presented itself recently in an interesting case that my colleagues and I had the opportunity of studying and which is presented here in some detail.

## REPORT OF A CASE

*Hereditary Background.*—The patient's paternal grandfather and grandmother were first cousins. A paternal uncle, C. R. B., was a patient in the Taunton State Hospital from 1904 to 1910, having been admitted at the age of 19; the diagnosis was dementia praecox. He had numerous fantastic delusions and hallucinations and complained of occasional vertigo and headache. Neurologic examination revealed hyperactive patellar and biceps reflexes and absence of abdominal and cremasteric reflexes. He was inclined to assume strained awkward positions and exhibited flexibilitas cerea. No neurologic diagnosis was made. He had periodic convulsive seizures and died during a convulsion which followed an attack of diarrhea and vomiting. No autopsy was done. Most of the patient's other near relatives lived to an advanced age, without evidence of nervous or mental disease.

*History.*—The patient, C. H. B., was born in Massachusetts on Sept. 23, 1914, after a prolonged, difficult labor, which was terminated by instrumental delivery. Early development was normal, and the patient was singularly free from disease except for whooping cough during childhood. He was considered an excellent student but was forced to stop in the first year of high school, with the onset of the present illness.

The patient was considered normal until the fall of 1929, when he began to negelect his studies, seemed unable to concentrate and was finally forced to quit, near the end of his first year in high school. After that he seemed more preoccupied, said little, read considerably and preferred solitude. He grew more and more reticent and finally refused altogether to speak to his father, although the home life had previously been congenial. One day he appropriated some money and ran away to a neighboring town, where he was apprehended. He was admitted to the Boston Psychopathic Hospital on Oct. 9, 1931, and was discharged as improved on November 14.

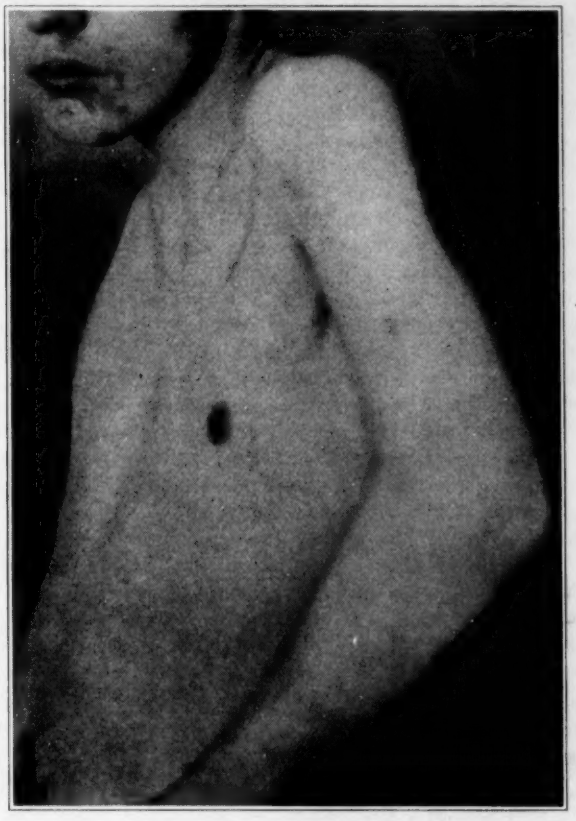
*Course at the Boston Psychopathic Hospital.*—Physical Examination: The patient was a thin, tall youth aged 17, with dry skin and shocky hair, no hair on the chest and thin hair on the hands. Much subcutaneous fat was present in the mammary region (compare with later findings). The pupils were widely dilated and reacted normally; the patellar reflexes were hyperactive; there were frequent slight involuntary jerks of the arms and legs, which were irregular and sudden; he had cold, sweating hands and feet. The blood pressure was 168 systolic and 82 diastolic. The ocular fundi were normal.

Roentgenogram of the Skull: The sella and sinuses were normal. No evidence was noted of increased intracranial pressure or other pathologic change.

Laboratory Data: The blood serum and the spinal fluid showed no evidence of syphilis. Urinalysis on October 10 revealed no abnormality except the slightest possible trace of albumin. Urinalysis on November 1 gave normal results. Hematologic examination showed a hemoglobin content of 85 per cent (Tallqvist) and 8,800 white cells. On October 15 the nonprotein nitrogen was 33.3 mg. per hundred cubic centimeters, and the curve for sugar tolerance was normal. On October 10 examination of the cerebrospinal fluid showed: 30 cells (lymphocytes) per cubic millimeter, globulin 1 mg., total protein 105 mg. and sugar 65 mg. per hundred cubic centimeters. The colloidal gold curve was 0013000000. On October 14 the cerebrospinal fluid contained no cells; no globulin, and 62 mg. of total

protein and 73 mg. of sugar per hundred cubic centimeters. The colloidal gold curve was 0011100000. On October 17 the basal metabolic rate, based on the average of three tests, was minus 3.5 per cent.

Mental Status: The patient was quiet, docile, cooperative and clean. He showed lack of initiative and psychomotor activity. Speech had a peculiar intonation and was almost dysarthric. The mood was moderately depressed. He had vague, unsystematized delusions that his family and teachers did not understand him, talked about him and laughed at him. He expressed antipathy toward



Photograph of C. H. B., taken in April 1936. The prominent lips, atrophied muscles of the chest and shoulder and projecting scapula are well shown. Note that practically only the deltoid muscle is left intact in the shoulder girdle. Compare the disparity in size between the normal forearm and the atrophied shoulder girdle.

his parents. No hallucinations or compulsive phenomena were evidenced. The sensorium was fairly clear; the scope of general information was good, and insight was fair. The intelligence quotient was 92.

Diagnostic Impression: The patient showed a schizoid reaction but no evidence of deterioration. The neurologic signs pointed toward an unstable sympathetic nervous system. Tumor of the brain was ruled out. Bradykinetic movements,

disturbance of the vasomotor system, increased seborrhea over the face and change in personality since the age of 15 suggested a possible lesion of the tuber cinereum, perhaps on the basis of an inflammatory process.

*Subsequent Course.*—After his discharge from the Boston Psychopathic Hospital, the patient refused to speak to his father. There developed symptoms of restlessness and somnolence, which recurred at intervals. About November 1935 there developed inversion of the normal sleep rhythm, in that he was unable to sleep at night but appeared somnolent during the day. One evening he became impulsive and excited, striking his father and mother. He was admitted to the Taunton State Hospital on the following day, December 25.

*Course at the Taunton State Hospital.*—Physical Examination: The results of examination were similar to those recorded at the Boston Psychopathic Hospital with, in addition, the maintenance of strained, awkward postures and flexibilitas cerea. A low grade fever was present on admission.

Laboratory Data: Hematologic examination on Jan. 11, 1936, showed a hemoglobin content of 105 per cent (Sahli), red cells 4,500,000 and white cells 11,750, with 85 per cent polymorphonuclears, 7 per cent lymphocytes and 8 per cent mononuclears. On January 13 the cerebrospinal fluid showed a trace of albumin and of globulin, no cells, sugar 59 mg., and chlorides 820 mg. per hundred cubic centimeters. The colloidal gold curve was 0012331000. On April 2 there were a heavy trace of albumin, a trace of globulin, no cells and a colloidal gold curve of 0000000000.

Mental Status: The patient was manneristic, exhibiting odd, uncomfortable attitudes and facial grimaces. He was in good contact with reality. There was a general lack of initiative and spontaneity. He was seclusive and dull. No definite delusional trends were elicited, although he still expressed antipathy toward his parents. He mentioned vague hallucinations of sight. The sensorium was fairly clear, but the thinking capacity appeared to have undergone some deterioration, as evidenced by an intelligence quotient of 68, with considerable scattering. Because of the history of change in personality, evidence of splitting, affective dulling and catatonia, a tentative diagnosis of catatonic or hebephrenic dementia praecox was made, although it was thought at the time that this did not explain the entire picture.

*Subsequent Course.*—After admission the patient continued to have a low grade fever and appeared drowsy and apathetic, although he could easily be aroused and was in good contact with his surroundings. After a few days the temperature began to show daily rises to 103 F. He perspired profusely from the neck up, but the remainder of his body was dry. At times he was incontinent of the bowels and bladder. Examination of the ocular fundi revealed definite hyperemia of both optic disks, but no elevation. It was noticed that he was unable to raise the right eyelid. A spinal puncture on January 13 revealed a distinct initial elevation of pressure to 38 mm. of mercury (the findings otherwise are recorded with the laboratory data). On January 14 the temperature suddenly dropped to normal, the elevation having lasted twenty-one days. The patient was gradually allowed to be up and about, but he preferred to sit in one place, assuming awkward, distorted postures. The ptosis of the right eyelid gradually disappeared.

An amazing and subtle change began to appear; in a note made on April 6 it was recorded that his posture and general appearance were beginning to exhibit evidences of severe dystrophy, dystonia and asymmetry of the entire body, especially marked in the upper region, which appeared distinctly "lop sided." The muscles of the lips appeared prominent, giving him a "tapir mouth"

appearance. There was marked wasting of the muscles of the left shoulder girdle and chest, with winging of the scapula. These findings were less marked on the right side. The left arm was flexed at the elbow, which was beginning to show limitation of motion. Fibrillary tremors were present in the involved muscles.

## COMMENT

The findings are shown in the accompanying illustration. Clinically, the syndrome bore a marked resemblance to the Landouzy-Dejerine (facioscapulohumeral) type of progressive muscular dystrophy. Occasionally the latter is confused with the Aran-Duchenne type of atrophy; it may, therefore, be interesting at this point to compare these conditions in relation to the picture in our case.[4]

It would seem, when these conditions are compared point by point, that our patient presented a clinical picture almost identical with facioscapulohumeral muscular dystrophy. Yet we could not believe that it was idiopathic. The peculiar onset, fever, somnolence, transient ptosis, abnormal spinal fluid and fibrillary twitchings pointed strongly to a more central disease process, undoubtedly encephalitic in origin. But how could encephalitis produce a syndrome such as this? If one accepts the common theory that the essential pathologic change of progressive muscular dystrophy is in the muscle fibers, this is a difficult question to answer. Fortunately, however, another explanation is forthcoming. Ken Kuré[5] and his co-workers have applied to the dystrophies their conclusions that the parasympathetic nerve supply passes antidromically in the posterior roots to somatic muscles. They expressed the belief that the myopathies are due primarily to lesions of the parasympathetic nervous system and have reported studies on man as proof. If this is true—if there is any evidence that progressive muscular dystrophy may occur as the result of involvement of the parasympathetic nervous system or of any other type of nerve lesion, it is not unreasonable to postulate that encephalitis, which is capable of involving any part of the central or peripheral nervous system, may thereby create a myopathic syndrome such as I have described. Undoubtedly, in more than one case progressive muscular dystrophy has been called idiopathic in which, on closer analysis, it would have been found to be encephalitic, and it is my opinion that such an etiologic relationship should be kept in mind.

This line of reasoning aided considerably in a proper evaluation of this case, although my colleagues and I were loath to accept it merely as a *post hoc, ergo propter hoc* conclusion. Therefore, in order to differentiate still further between a myogenic and a neurogenic origin, we made determinations of the creatine-creatinine metabolism in conjunction with the ingestion of amino-acetic acid, following the procedure described by Tripoli and his co-workers.[6] The subsequent

4. Electrical reactions are omitted.

5. Kuré, K., quoted by Grinker.[1]

6. Tripoli, C. J.; McCord, W. M., and Beard, H. H.: Muscular Dystrophy, Muscular Atrophy, Myasthenia Gravis and Strabismus: Clinical and Biochemical Studies of the Effects of Amino Acid Therapy, J. A. M. A. **103**:1595 (Nov. 24) 1934.

interpretation is based on the observation of these and other writers that the patients who showed the most improvement were those in whom the average increase in creatinuria after amino-acid therapy was begun was more than 50 per cent above that of the period used as a control,

| Aran-Duchenne Type | Landouzy-Dejerine Type | Syndrome in Our Case |
|---|---|---|
| 1. History of familial or hereditary involvement is uncommon. | 1. Hereditary or familial. | 1. Suggestive heredity (uncle's case). |
| 2. Usually begins in the third decade; rarely before the age of 20. | 2. Begins during childhood or puberty. | 2. Onset at age of 21. |
| 3. Starts with weakness and atrophy in the small muscles of the hand; may go on to claw hand, owing to contractures of antagonistic muscles; gradually extends up the forearm, arm and shoulder girdle; deltoid and biceps muscles are usually severely damaged, while the triceps muscle is less involved; muscles of the neck are usually implicated. | 3. The shoulder girdle is implicated before the distal portion of the extremity; the facies are thick and mask-like, with little play of expression; the lips show pseudohypertrophy and thickening; the muscles of the forearm, hand and back tend to remain normal; contractures are common. | 3. Began with atrophy of muscles of the left shoulder girdle, followed by involvement of muscles of the chest, winging of the scapula and "tapir mouth" due to prominence of the orbicularis oris muscle; the neck, forearm and hand were not implicated; contracture of the elbow joint; triceps muscle severely affected, deltoid muscle less so. |
| 4. The process is usually symmetrically bilateral. | 4. Involvement is not always symmetrical. | 4. The left side much more affected than the right. |
| 5. Atrophy is accompanied by fibrillary tremors. | 5. No fibrillary tremors occur as a rule, although cases have been reported. | 5. Fibrillations present. |
| 6. The radial, periosteal, biceps and triceps reflexes become reduced in degree and, in correspondence with the degree of atrophy, are finally lost. | 6. Reflexes are usually markedly reduced and at times are lost. | 6. Decreased reflexes. |
| 7. No trophic or sensory changes. | 7. Sensation is usually unaltered. | 7. Sensation intact. |
| 8. Progression is extremely slow, and years may elapse before atrophy of the shoulder girdle is complete. | 8. Lasts many years, and the patient may live to an advanced age. | 8. A chronic wasting process, beginning in the shoulder muscles. |

provided this increase in creatinuria disappeared in a few weeks; such a course of events occurred most commonly in the primary myopathies and in myasthenia gravis. Conversely, persons who showed little or no increase in creatinuria above that of the control period exhibited the least improvement or none at all; this was likely to be true particularly in muscular atrophy that was far advanced or was secondary to nuclear or peripheral nerve degeneration.

The patient was studied for twenty days. The daily excretion of creatine in the urine was determined [7] during a control period of five days in which no amino-acetic acid was given. At the end of this time the daily oral administration of 10 Gm. of amino-acetic acid in milk was begun, and the effect of its ingestion on the excretion of creatine was studied in twenty-four hour specimens of urine for three similar periods of five days each. The average results for each period are shown in the following tabulation.

| | Grams per 100 Cc. | Increase, Percentage |
|---|---|---|
| 1. Average excretion of creatine before the administration of amino-acetic acid (5/16/36 to 5/20/36)..... | 0.48 | .. |
| 2. Average excretion of creatine after the administration of amino-acetic acid | | |
| (a) First period (5/21/36 to 5/25/36)..... | 0.23 | 0 |
| (b) Second period (5/25/36 to 5/30/36)..... | 0.19 | 0 |
| (c) Third period (5/30/36 to 6/3/36)..... | 0.17 | 0 |

As the results indicate, the amount of creatinuria that was present during the control period, in which the patient received no amino-acetic acid, actually decreased after the ingestion of the amino-acid, a finding that would tend again to place our case in the group of myopathies secondary to nerve degeneration. Furthermore, it is important to note that during the entire period of administration of amino-acetic acid, about a month, the patient's symptoms, both mental and physical, became conspicuously worse. The atrophy increased, the stiffness of the muscles grew more pronounced and he became exceedingly torpid in thought and action.

Accordingly, amino-acetic acid was discontinued, and the patient was given a so-called postencephalitic regimen, consisting of ascending doses of stramonium, graded outdoor exercises and hydrotherapy. Under this regimen he improved remarkably. At the time of writing, he is up and about and in good contact with his environment. He is cooperative, seems more optimistic about the outcome of his illness and, in fact, has been promised a trial visit home in the near future.

No definite conclusions can be drawn from a single case. My purpose here is rather to corroborate and add to the findings of others. Much additional work is necessary to prove or disprove the rôle of encephalitis in the causation of the myopathies. It will be interesting to follow any developments that this new line of reasoning may engender.

## CONCLUSIONS

1. A sequel of epidemic encephalitis, not previously described in the English literature, is herewith presented, namely, a syndrome simulating the Landouzy-Dejerine type of progressive muscular dystrophy.

7. Benedict, S. R., and Myers, V. C.: The Determination of Creatine and Creatinine, Am. J. Physiol. **18**:397, 1907. Folin, Otto: On the Determination of Creatinine and Creatine in Urine, J. Biol. Chem. **17**:469, 1914.

2. That the condition in this case was neurogenic rather than myogenic appears to be indicated by the postencephalitic onset, fibrillary twitchings, atypical creatine metabolism and exacerbation rather than relief of symptoms following the ingestion of amino-acetic acid.

3. Although definite conclusions cannot be drawn from a single case, nevertheless the findings seem to corroborate recently reported evidence that the dystrophies are in reality the result of certain nerve lesions rather than being primarily myopathic, as is commonly supposed.

4. In all probability, progressive muscular dystrophy is occasionally termed idiopathic in cases in which closer analysis would have revealed the encephalitic origin, and it is my opinion that such an etiologic relationship should be kept in mind.

Dr. D. G. Henderson assisted in the technical procedures involved in the determinations of the creatine-creatinine metabolism.

# DISTURBANCES OF ACTIVITY IN A CASE OF SCHIZOPHRENIA

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This article is one of a series of reports on studies of a certain psychopathologic picture occurring in schizophrenia. It was previously observed that some schizophrenic patients present a number of symptoms which are not likely to occur alone but are observed only in association with each other. The association of these symptoms in a consistent fashion seems to be indicative of a hitherto undescribed syndrome and therefore to merit closer study.

The principal components of the syndrome in question are: 1. Severe disturbances of self-awareness: These are manifested in a great variety of complaints, of which the most important is the impression of being divided into two or more persons, and various symptoms of depersonalization.

2. The experience of motor influences and the impression of passivity: This disturbance is manifested in such complaints as: "They move my arm." "It is not I who is talking; the words just fly out from my mouth; it doesn't take any effort." "I feel like a mechanical man."

3. Certain somatic complaints: Examples are the impression that the inside of the body is empty, that the body is too light or too heavy, that the patient is flying or standing on his head, that the body is suddenly growing or shrinking or that some airy substance is passing through the body and emanating from it.

4. Auditory hallucinations with endosomatic localization: The patients say that hallucinatory voices come from within their bodies. These voices are frequently referred by the patient to small human beings (lilliputians) who are felt to reside in their bodies.

Several features of this symptomatology and the interrelations between its various components have been previously studied.[1] The particular disturbances of activity which will be discussed in this paper do not represent a consistent feature of the group as a whole, but are seen only in patients in whom the symptoms are most pronounced.

The comment will be limited to one case which shows in a clearcut form the disturbances of activity in question.

The patient was admitted to the Worcester State Hospital in 1926, the diagnosis being schizophrenia. Since Oct. 1, 1933, daily observations have been made. The description which follows refers to the clinical picture up to June 1935. The

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From the Research Service of the Worcester State Hospital.

1. Angyal, A.: (*a*) The Perceptual Basis of Somatic Delusions in a Case of Schizophrenia, Arch. Neurol. & Psychiat. **34**:270 (Aug.) 1935; (*b*) The Experience of the Body-Self in Schizophrenia, ibid. **35**:1029 (May) 1936; (*c*) Phenomena Resembling Lilliputian Hallucinations in Schizophrenia, ibid. **36**:34 (July) 1936.

patient's general condition then changed to some extent, and the disturbances of activity, though still present, were not as marked as they had been up to that date.

The following examples of the patient's behavior are characteristic.

If the patient is left alone, he stands all day in a corner of the ward. His posture is relaxed; his face is pale and somewhat ironed out, and the number of expressive movements of the facial muscles is greatly reduced. Closer observation shows, however, that his attitude is significantly different from that of the usual catatonic picture. He remains motionless for long periods; then suddenly it seems that he wants to start to do something. He takes one or two steps forward and then suddenly steps back to where he had started. He repeats this a number of times and then starts to go in some other direction, but after a few steps he again suddenly returns to the original place. His whole behavior gives one the impression that he is trying hard to start some activity and is fighting against something which holds him back but cannot overcome the hindrance. He becomes more and more excited, angrily mumbles a few words and finally gives up the fight; sometimes with a gesture of resignation he remains standing quietly for a period and then repeats the whole cycle of behavior.

If the patient is asked to do some simple task, he shows a marked initial psychomotor retardation but then performs it in an automatic fashion, apparently as well as he can. For example, if he is asked to push a swab he behaves in a way similar to that of the spontaneous attempts already described. He takes a step forward and then steps back, so that the same spot rather than the corridor is swabbed. The slightest interference is sufficient to interrupt his activity. Some noise or a passer-by attracts his attention, and he immediately stops working. If he is asked to go with the examiner, he does so, but he stops a number of times as if held back by some hindrance. He makes some effort to continue walking, but usually he does not succeed unless the instruction is repeated. His activity in general is of short duration; one gains the impression that one reason for this is that his impulse for activity is exhausted in a few seconds.

By frequent observations it was ascertained that the interruptions of activity are not random but are often definitely related to certain factors in the external situation, as follows: 1. The patient's attention is easily attracted by anything going on around him, e. g., a noise or a passer-by. When his attention is attracted by such disturbing factors, he immediately stops his activity.

2. The patient's activity is also immediately interrupted when the situation involves even the remotest possibility of a choice. It was observed that when he goes by an open door he stops, perhaps takes a side step toward the door, hesitates, and starts alternately to continue his way and to go into the room. Finally he does neither. Such behavior is even more marked in the following situation: In the ward there is an intersection of corridors. When he has to go through this place he takes one step toward one direction and then a step toward another and so on. He seems unable to act on any of the four possible ways from which he must choose. In this situation he gives one the impression of a puppet pulled in different directions by invisible strings. These and similar examples indicate that certain situations which suggest some activity—such as the open door which suggests that he enter the room or an intersection where several ways are open to choice—easily affect his behavior. One can state that he is abnormally susceptible to the suggestive quality of situations ("demand quality," K. Lewin).

3. The patient's activity is subject to interruption also when a change in his activity is demanded. For example, when he is asked to come with the examiner to his office he does so, but when he arrives at the corner of the corridor where he must make a turn he stops and steps back and forth. He seems to struggle with some difficulty, and usually he cannot go around the corner until he is told to do so specifically. It seems that a required change in activity, such as a new task, is too difficult for him. When he arrives at the door, a new problem arises for him, namely, to cross the threshold. For a long period he steps forward and then backward, until finally he enters the room. Similar behavior is exhibited before he sits down. He makes a move to sit down, then straightens up again, repeating these movements until he is specifically told to do one or the other.

These last examples show also that it is not sufficient merely to give a certain command to the patient, but that every detail of the desired action must be separately demanded of him. For example, it is not sufficient to tell him that he may leave the room. He must be told to stand up, to walk, to open the door, etc. If he is instructed in every detail he is able to work almost continuously. An example of this is given in the fact that he is able to play table tennis fairly well, apparently because the situation is such that it repeatedly suggests what to do next. The ball thrown toward him defines the next action—to hit it back. Besides this, possibly it does not allow time for him to hesitate. At one time another patient became interested in him and wanted to get him to work. He gave him a swab and followed him with another. Whenever he stopped, the other patient was right at his heels with his swab, and in this way forced continuation of the work. Under these circumstances he was able to swab for hours.

The patient realizes that he can do things more easily if he is told to do them, and therefore he is anxious to receive orders. Sometimes he says that he needs a "boss" who would always stand near him and tell him what to do. By way of an experiment, parole privileges which allowed him to leave the ward were granted. However, he did not take any advantage of this privilege, and when asked why, he said that it was of no use for him to have parole if he were not told to leave the ward; he said he would be able to use this privilege if he could have a written order, which he could read whenever he wanted, telling him to leave the ward. This request was granted, but it was of no help to him, since he could not exhibit sufficient spontaneity to take the note from his pocket and read it!

The patient tries almost to force definite instructions from outside as to what he should do. Thus, for example, if at the end of an interview no definite instruction is given as to where he should go, he asks for this instruction in some indirect way.

Even strong physical needs are often not sufficient to stimulate spontaneous activity in the patient. Once during an interview he showed signs of physical discomfort. He was asked what the trouble was, and he answered: "Something was flying around in the air. Some physical pills were flying around, pills which make you go to the toilet." Then he continued, almost crying," Some SOS is flying around in the air." He hinted in this roundabout way that he needed to go to the toilet. He was told to do so. When he reached the door, though it was apparent that he was in the greatest discomfort, he looked back and asked, "You mean I should go this way?"

Another characteristic example of the patient's behavior is the following: It was observed that he was carrying about pieces of useless paper in his pocket. When questioned concerning this, he stated that another patient had put the pieces of paper in his hand, and since he could not decide to throw them away, he had

kept them. He was asked: "Is it so difficult to throw away a piece of paper? You could do it easily." In the meantime a piece of paper was passed to him, which he took automatically, and the conversation was turned to some other topic. He started to put the paper into the waste-basket, which was near his chair, then took it back again, then started to put it on the desk and finally took it back and looked at the examiner, apparently waiting for some instruction. He struggled in this manner during the rest of the interview. When told at the end of the interview that he might go, he was very hesitant and finally asked, referring to the paper: "Should I. . . .?" He was told that he might do just as he liked. An hour after the interview he was seen standing in the corridor with the paper in his hand, with an expression suggestive of great indecision.

When the patient is asked to write something but is not told to put down the pencil, he starts to put it down but takes it up again, repeating this for a long period. Once, for some experiment, he was asked to put his hand on the desk for a few seconds. After the experiment he took his hand off the desk, but after half a minute it went back almost automatically to the desk and then off again. This was repeated several times, until he was instructed to take his hand off the desk.

The same indecision is manifest not only in the patient's overt activity but also in his verbal expressions. He seldom gives a definite answer when he must decide between two possibilities, but his answers have a stereotyped structure, as, "Some . . . yes but some . . . no" or "In one way . . . yes but in the other way . . . no." Instead of a definite "yes" or "no," he answers mostly with "may be." It is remarkable that he seldoms says "I will" but says instead: "It is up to me" or "I am supposed" to do this or that.

### COMMENT

Reviewing the patient's behavior, it may be stated that the following are the most outstanding features of the disturbances of his activity:

1. Marked inactivity due to some kind of inhibition which the patient tries hard to overcome, but in which he cannot succeed. Spontaneous activity is especially difficult for him. He is somewhat more successful when he is definitely instructed what to do.

2. Great difficulty in the initiation of activity or in the making of a new "turn" in activity which has already been started.

3. Easy interruption of the initiated activity, either by exhaustion of the impulse or by any interference from outside. These factors may be looked on as distracting external factors or as suggestive qualities (demand character) of the situation. There is extreme accessibility to any type of suggestion—a verbal suggestion or a suggestion arising from the situation itself. There is an attempt to respond with some activity to the slightest suggestion, but there is inability to follow it through.

4. Inability to make a decision when the situation involves the possibility of choice.

The interpretation of the picture seen in this patient can be attempted only in relation to the general psychopathologic background, of which these disturbances of activity form only one aspect. As stated previously, he presents a typical example of a kind of schizophrenic picture which is characterized by a certain constellation of symptoms. Several features of this symptom complex were reported previously, and an

attempt was made to show that all of them are due to a basic disturbance of self-awareness. It will be shown in the following discussion that the disturbances of activity described here can also be understood on the same basis.

The disturbance of self-awareness consists in a faulty discrimination between the ego and the external world. Certain components which normally are included in the self are not experienced by these patients as parts of the person, but are referred to the external world. In such cases one may speak of a disruption of ego-reference. My patient, for example, frequently complains that parts of his body do not belong to him, that they disappear, that his arms and legs are dead or that his teeth do not feel "natural" but feel as if they were "not grown in but only set in." He often does not experience his own actions as his own but regards them as something done to him from without. He feels himself like an automaton and as a prey of some foreign forces over which he has no control. He complains that he cannot think but that others use his head, that it is not he who is speaking but the words fly out from his mouth. Once he stated that he does not laugh, that laughter does not come from his "system," but only his "skin laughs." "They" interfere with his movements; "they" move him around; "they" make his feet go; "they" stop him; "they" start him, and so on. He calls such movements "extra motions," and explains this as a surplus of activity which occurs in the course of his consciously intended movements. Another manifestation of such disturbed self-awareness consists in the impression of being divided into many persons or into many "images" or "figures" which interfere with each other. He complains, for example, that "there is an extra one, another A. D.," and that he is not able to do anything unless he gets rids of the other A. D.

To regard the complaints which I refer to a disturbance of self-awareness merely as false beliefs, or delusions, seems to be an avoidance of the real issue. One must give credit to a large extent to the patient's statements. The experience of self-awareness is an (incomplete) conscious picture, a symbolic representation of the actual state of the total personality. When the self-awareness is disturbed, one is justified in assuming an underlying disturbance of the personality. Thus, when a patient experiences himself as an aggregate of disconnected fragments, one should not regard his statement merely as a false belief but should consider that the unity of the personality structure is impaired or disintegrated. In another paper [1b] it was pointed out that the loss of ego-reference can be understood from the psychologic point of view as a special kind of defense mechanism against such factors as are not compatible with the rest of the personality. The particular nature of this defense mechanism can be best stated if one compares it with the mechanism of hysteria. In hysteria such factors as are not compatible with the rest of the personality are excluded from consciousness; they are "repressed" (anesthesia, amnesia, etc.). In the type of schizophrenic patient with whom I am dealing here, on the other hand, the disturbing factor is allowed to enter consciousness, but its "belongingness" to the ego is not recognized and is ascribed to influences from the outside.

According to this view, when a patient complains that he is divided into many persons or that he experiences motor influences, one can take

it as an indication that the unitary organization of the personality is actually broken off and that he is at the mercy of mutually exclusive conflicting tendencies.

Normal activity presupposes the unity of the person. My patient's disturbances of activity can be made understandable on the basis of the impaired unity of his organization of personality. For this purpose the case will now be reviewed in the light of the patient's own statements with regard to his difficulties. The way he experiences his difficulties will supplement the objective account of his behavior which was given previously and will give indications as to the source of his disturbances of activity.

The patient ascribes his difficulties to the fragmentation of his personality. The following verbatim statements of the patient illustrate this: "I can't do any work because I am only half. I am 50 per cent somebody else." "How can I do anything if I am disconnected, shot all to pieces?" Once when he was struggling to enter the examiner's office and was stepping backward and forward in the previously described manner, he was asked, "Can't you make it?" and he answered: "I could, but I have half a dozen others to carry."

The impairment of the personality organization brings about the disturbances of activity by the following two mechanisms:

1. These impulses, which have become dissociated (have lost their ego-reference), interfere with the patient's conscious intentions. The patient is greatly confused and inhibited by the large number of contradictory impulses. For example, he says: "When I want to go to bed I know I shouldn't." His impulses are usually projected. He said for instance: "They want me to go one way, and at the same time they want me to go the other way." At another time he said: "They keep telling: 'Yes, no, yes, no.' What can I do?"

In most instances the dissociated impulses are experienced by the patient as motor influences. The dissociated tendencies have control to a considerable extent over the motor functions. They induce various movements which greatly interfere with his intentions. He complains that he cannot act normally because "they pull back on me;" "the force is the other way;" "they make my feet go in the wrong direction," or "they throw me out sideways." Once he complained in the following manner: "They move my hand, and I don't like it. They get me mad. Somebody is here who is stronger, bigger than I am. He knocks me out every five minutes. He just knocks me flat." He says that whenever he starts to do something "They jump in," "stop me," "turn me around" or "push my whole frame aside."

As these examples show, the patient refers the impairment of his activity to specific interfering influences (dissociated tendencies) over which he has no control.

2. The disintegration of the personality organization also induces a general weakness and instability of impulses. Free flow of activity presupposes the unified organization of personality. A single action is not an independent entity. It is differentiated out of the total personality, from which it derives its strength. It is the organic outgrowth of the personality background, comparable to the terminal branch of a tree. When dissociation takes place, that is, when a

single impulse is "cut off" from the personality "tree," its matrix, it loses its strength; it becomes feeble and unstable. In other words, when the subject becomes a battlefield of dissociated conflicting tendencies, his impulses lack the necessary energy and his volitions are half-hearted, since they are not backed up by an undivided personality.

The patient feels that his difficulties of activity are largely dependent on the weakness of his impulses. It is on this ground that he explains his difficulty in initiating activity or in making a decision. He says that he does what "they" tell him to do because he himself "can't raise my vitality high enough to do what I should do." He has on occasion said: "I am nothing. They rub me out. Somebody else got my name, and when I want to use it I can do nothing." Even when he succeeds in starting some activity, his impulse does not last long, but fades away in a few seconds. Examples of this complaint are: "When I start to do something they abstract it from me; they take it out of my head. I don't forget it. It leaves me. It is blown out just like the wind." On another occasion he said, "If I have the inclination to do something, they yank it all out." "I can't do anything because I can't hang onto the feelings long enough; they don't stay with me long enough."

The patient's impulses are often so vague and indefinite that he is unable to grasp them clearly. This is indicated by such statements as the following: "I hear them tell me to go, but I don't know where." "They tell me what to do, but I can't hear it well." The inertness and indefiniteness of the impulses also make it understandable why the patient is so anxious to obtain definite instructions as to what he should do. He needs support from outside to give more definite direction to his lazy impulses. He comments on this point in the following way: "If I want to do something I can't, it doesn't affect, it doesn't penetrate, but if you tell it to me that gives me a push."

The fact that the patient is extremely accessible to every kind of distracting influence can also be explained by the weakness and instability of his impulses. Ach pointed out that voluntary activities presuppose a certain mental set which he called *determinierende Tendenzen.* This mental set enables the subject to proceed toward a set goal in spite of interfering factors which otherwise would make him deviate from the original goal. They form a defensive barrier against distracting factors. *Determinierende Tendenzen,* however, which originate from an extremely feeble impulse cannot offer a sufficient resistance, and the patient will deviate from his goal, or his activity will be interrupted by the least provocation, as by distraction of attention, suggestive quality of the situation, etc., of which several examples have been given.

The patient's behavior also shows a great number of apparently "manneristic" activities, the discussion of which has been omitted here. In a previous study it was shown that these are reactions to abnormal bodily sensations which are an outstanding feature in the patient's symptom complex. He has, for example, the impression that some substance is leaving his body, and he makes movements to catch it. He feels also that the ground swells up under his feet or that he is sinking into the ground, circumstances which make his gait insecure. This type of phenomenon has been discussed in more detail in previous papers.

SUMMARY

The disturbances of activity of certain schizophrenic patients have been studied over a long period, and extensive objective observations of one patient's behavior are presented. The spontaneous comments of the patient, which throw light on the way in which he experiences his difficulties of activity, are incorporated into the clinical material.

The following are the most outstanding features of these disturbances of activity:

1. Marked inhibition of activity, which the patient tries hard to overcome, but without success. Spontaneous activity is especially difficult for him. He is somewhat more successful if he is specifically instructed what to do.

2. Great difficulty in initiating activity or in making a new "turn" in activity which has already been started.

3. Easy interruption of the initiated activity, either by exhaustion of the impulse or by interference from the outside, such as distracting external factors or suggestive qualities (demand quality) of the situation.

4. Inability to make a decision when the situation involves the possibility of choice.

The explanation of the patient's difficulties has been sought in a disruption of the unitary organization of personality which is experienced as a disturbance of self-awareness, more specifically, as a loss of ego-reference of the experiences. The lack of unity of the personality organization induces the disturbances of activity by two different mechanisms: On the one hand, the patient's intentions are interfered with by the dissociated tendencies; on the other hand, his impulses are too feeble and unstable because they lack the support of an undivided personality.

# NEURO-EPITHELIAL CYST OF THE THIRD VENTRICLE

## Report of a Case with Recovery Following Operation

W. James Gardner, M.D., and Oscar A. Turner, M.D., Cleveland

While cystic tumor of the third ventricle cannot be considered rare, it is distinctly uncommon and the literature contains reports of few cases. Rehbock [1] stated that only fifty-three authentic cases have been described, and he reported three additional cases. In addition, he listed the cases reported since the reviews of the literature by Zimmermann and German,[2] Stookey,[3] and Dandy.[4]

Clinically, the signs and symptoms of obstructive tumor in the region of the third ventricle are variable. Sudden death is common, especially when the tumor is cystic, and the diagnosis in most of the reported cases was made at autopsy. Although some writers have attempted to elucidate a diagnostic clinical syndrome, most authors agree with Fulton and Bailey,[5] who emphasized the fact that there is no characteristic syndrome of lesions of the third ventricle per se but that whatever localizing evidence is present is due to the effects of pressure on the adjacent cerebral tissue.

A case is reported in which there were no localizing signs or symptoms, the diagnosis having been made from ventriculographic studies alone.

### REPORT OF CASE

A white woman aged 31 was admitted to the Cleveland Clinic Hospital on June 4, 1936, complaining of frontal headache, decreasing vision and nausea. She had been well until August 1935, when severe occipital headaches began to develop; these usually occurred two or three times a month. Nausea and vomiting were not associated with the headaches, and at that time examination of the eyes revealed little of significance, though there had been some decrease of vision. In general, the patient seemed to be well. There was a history of chronic indigestion and gastric pain, which were unassociated with food or meals.

In February 1936 the patient fell on the ice, striking the right occiput and the right hip. She experienced severe lancinating pain for a few minutes over

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From the Cleveland Clinic.

1. Rehbock, D. J.: Neuro-Epithelial Cyst of the Third Ventricle, Arch. Path. **21**:524-530 (April) 1936.

2. Zimmermann, H. M., and German, W. J.: Colloid Tumors of Third Ventricle, Arch. Neurol. & Psychiat. **30**:309-325 (Aug.) 1933.

3. Stookey, B.: Intermittent Obstruction of Foramen of Monro by Neuro-Epithelial Cysts of Third Ventricle: Symptoms, Diagnosis and Treatment, Bull. Neurol. Inst. New York **3**:446-500 (March) 1934.

4. Dandy, W. E.: Benign Tumors in the Third Ventricle of the Brain, Sprinfield, Ill., Charles C. Thomas, Publisher, 1933.

5. Fulton, J. F., and Bailey, P.: Tumors in Region of Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**:1-25 (Jan.); 145-164 (Feb.); 261-277 (March) 1929.

the back of the head, and although she was dazed at the time she was not unconscious. During the next two weeks severe pain occurred in the lower part of the back and the hip, but pain in the head was absent. Roentgenograms taken later revealed a fracture of the skull extending parallel to and behind the frontoparietal suture on the left and backward nearly to the lambdoid suture. After the accident the suboccipital headaches became more severe and more frequent until they were almost constant. They were associated at that time with nausea but never with vomiting; often they were severe enough to awaken her at night.

About three weeks before admission, the patient was taken to another hospital, where ventriculographic studies were reported as indicative of a tumor of the third ventricle. After ventriculography, the headaches were entirely relieved. A short while before admission, they returned, but at that time they were frontal and less severe.

*Examination.*—Little was revealed of diagnostic significance. There were no defects of memory or of sensory or motor function. Speech was unimpaired, and auditory tests gave normal results. All cranial nerves were intact. Aside from bilateral papilledema of 1 diopter and enlargement of the normal blindspots, neurologic examination revealed no abnormalities. The pressure of the spinal fluid varied between 250 and 300 mm. of water.

In view of the absence of localizing signs, it was decided to repeat the ventriculograms. With the patient supine, lumbar puncture needles were introduced through drill openings which had been made in the left frontal and the right occipitoparietal region when the previous ventriculograms were made. Both ventricles were readily entered and appeared more superficial than usual. Ventricular estimation with sodium indigotindisulfate (indigo carmine) indicated free communication between the two lateral ventricles. Seventy-five cubic centimeters of fluid was removed from the ventricles, and air was substituted. After this the patient was placed in the sitting position, and 35 cc. of fluid was removed by lumbar puncture and replaced with 45 cc. of air. This injection of air was done to ensure satisfactory filling of the ventricular system below the obstruction.

The films revealed symmetrical dilatation of the lateral ventricles without displacement. The posterior part of the third ventricle could be visualized, while the anterior portion immediately behind and below the foramen of Monro was obscured by a filling defect.

The diagnosis made from the ventriculographic study was: tumor in the anterior portion of the third ventricle, with obstructive hydrocephalus. Immediate operation was considered advisable.

*Operation* (Dr. Gardner).—With the patient supine frontoparietal craniotomy on the right side was performed, exposing an extremely tense dura. The dura was opened widely by a crucial incision, and a cannula was inserted into the right ventricle to reduce the intracranial tension. A linear incision 4 cm. in length was made in the cortex just in front of the lower end of the motor area; this was carried into the lateral ventricle. A lighted retractor was introduced into the ventricle, and the fluid was removed by aspiration. The foramen of Monro was readily exposed, and the septum pellucidum was seen to bulge upward because of the fluid trapped in the dependent left ventricle. An opening was made through the septum with bayonet forceps, permitting the fluid to escape and the septum to collapse. This resulted in wider exposure of the foramen of Monro. The foramen was enlarged, measuring about 7 mm. in diameter; present in it was a smooth, glistening, rounded dark membrane, apparently the wall of a cyst.

The choroid plexus from the right ventricle traversed this bulging membrane and was slightly adherent to it (fig. 1).

After coagulation and severance of the attached choroid plexus, the foramen was enlarged by an incision carried in an upward and anterior direction. After this it was possible to extricate the cyst by gentle traction by means of forceps. During this procedure the wall of the cyst ruptured, and some thick pituitous

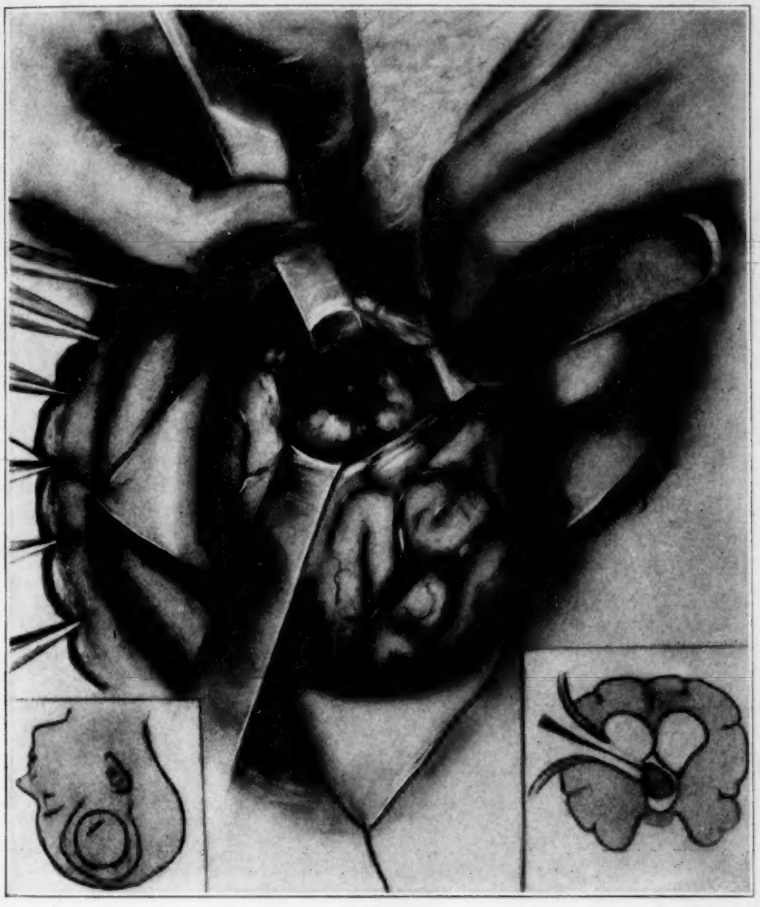

Fig. 1.—Drawing of the lesion as exposed at operation. The inserts illustrate the location of the incision into the lateral ventricle and the method of removal.

material was extruded. Hemostasis was completed by electrocoagulation and a few small muscle grafts. The ventricle was washed out repeatedly with physiologic solution of sodium chloride during the entire procedure. The wound was closed in the usual manner, and the patient left the operating room in good condition.

*Course.*—The course in the hospital was uneventful; the patient was discharged on the eighteenth postoperative day. When she was last examined, three months

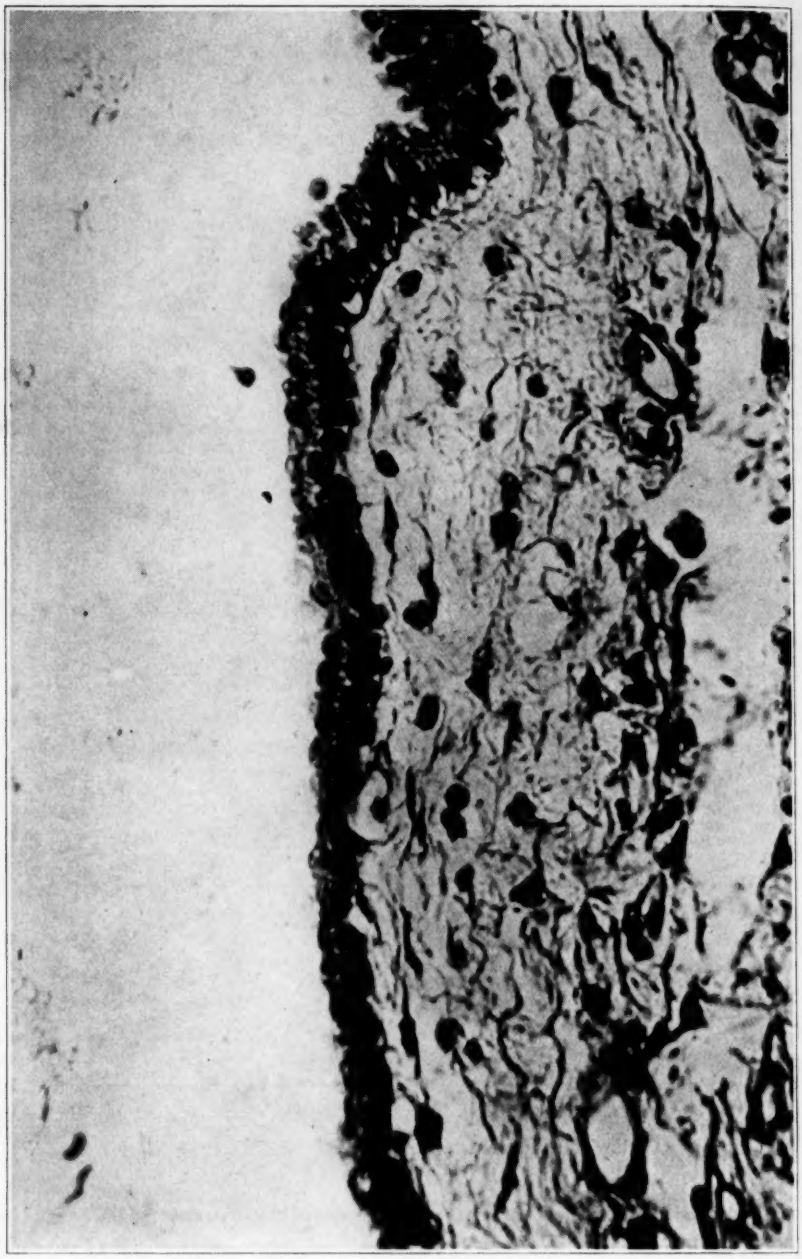

Fig. 2.—A section of the cyst wall, showing the type of lining epithelium. Hematoxylin and eosin; × 550.

Fig. 3.—A section of cyst wall (hematoxylin and eosin; × 120). Note the regional thickening, due in part to infiltrated round cells and erythrocytes.

after operation, she was free from symptoms and the choking of the optic disks had entirely subsided.

The postoperative diagnosis was: cystic tumor in the anterior portion of the third ventricle.

*Description of the Specimen Removed at Operation.*—Grossly, the specimen consisted of a partially collapsed cyst measuring 1.4 by 1 by 0.3 cm. The walls of the cyst were thin, transparent and shiny. Some attached tissue was present and was thought at the time to be adherent brain tissue.

Microscopically, the substance contained in the cyst was finely granular and homogeneous and took the eosin stain with a basophilic cast. Occasional groups of round cells, with small, compact central nuclei and a fair amount of vacuolated, granular cytoplasm were scattered throughout the contents.

The epithelial lining of the cyst (fig. 2) consisted largely of a single cell layer, although in some areas the cells were stratified to give as many as four indefinite layers. The cells themselves were for the most part cuboidal, with large, centrally placed, highly chromophilic nuclei, although occasional cells were seen in which the nuclear material was finely granular and lighter staining. There was a moderate amount of granular cytoplasm which was often vacuolated to an extreme degree. With the hematoxylin and eosin stain, the cytoplasm was acidophilic but had a basophilic cast. The cell boundaries were indistinct, and cytoplasmic inclusion bodies were not seen. The epithelium had a brush order, but definite cilia were not present. Blepharoplasts were not demonstrated.

The connective tissue wall varied greatly in thickness, in some places being very thin and in others thick owing to infiltrated collections of round cells and erythrocytes (fig. 3). The tissue was moderately dense and cellular, with a variable degree of round cell infiltration everywhere. There were numerous small vessels and capillaries filled with well preserved blood cells. The outer wall of the cyst merged inseparably with the choroid plexus, which in many places showed hyalinization of the connective tissue.

*Pathologic Diagnosis.*—The condition was diagnosed as neuro-epithelial cyst of the choroid plexus.

## COMMENT

Clinically, this case presents several points of interest. The absence of localizing phenomena, which Högner [6] and Hassin and Anderson [7] have noted when such a tumor is attached to the roof of the upper portion of the third ventricle, is significant. Zimmermann and German [2] have emphasized the localizing value of ventriculography in cases of tumor of this region, and the case reported here is additional evidence of the usefulness of this procedure.

Operative removal of a tumor of this type is not common, since death from acute hydrocephalus as a result of impaction of the cyst generally terminates the life of the patient, often before a diagnosis can be established. Of the five patients operated on by Dandy,[4] four recovered; one died of cicatricial stenosis of the aqueduct of Sylvius one month after operation. In all the thirty-one cases collected from

6. Högner, P.: Die klinischen Erscheinungen bei Erkrankungen des 3. Gehirnventrikels und seiner Wandungen, Deutsche Ztschr. f. Nervenh. **97**:238-266, 1927.

7. Hassin, G. B., and Anderson, J. B.: Cystic Tumor of Third Ventricle, U. S. Vet. Bur. M. Bull. **6**:56-61 (Jan.) 1930.

the literature by Dandy the diagnosis was made from necropsy material, no tumor having been diagnosed clinically. Zimmermann and German [2] have reported two cases, in both of which an operation was performed; one patient recovered and the other died before the final stage of a two stage removal could be completed. Rehbock [1] stated that twelve operations with nine cures have been reported.

The pathogenesis of this type of tumor is of extreme interest and is by no means completely understood. Most writers believe that it originates from the choroid plexus of the third ventricle. Some, however, consider that it originates from the ependyma, and while this cannot be totally contradicted, it is of interest that Zimmermann and German [2] pointed out that in the embryo the cells of the choroid plexus, as well as those of the ependyma, bear cilia. These writers expressed the belief that in certain rare cases such a tumor may arise from the paraphysis.

It is certainly true that in cystic tumor of the third ventricle the character of the cells, the papilliferous projections often seen in the lining epithelium and the close and often inseparable association with the choroid plexus more than suggest the choroid plexus as the site of origin.

# News and Comment

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The following physicians were granted certificates on June 2, 1937:

*After Examination.*—In Neurology and Psychiatry: Kenneth Ellmaker Appel, Philadelphia; Arthur Berk, Boston; Walter Bromberg, New York; Harold Otis Cozby, Chelsea, Mass.; Paul A. Draper, Colorado Springs, Colo.; Temple Fay, Philadelphia; James Charles Fox Jr., New Haven, Conn.; Edward David Hoedemaker, Seattle; David J. Impastato, New York; Abraham Adolf Low, Chicago; Robert Archibald Matthews, Philadelphia; John Hatcher Nichols, Cleveland; Johannes Maagaard Nielsen, Los Angeles; Leon Arthur Salmon, New York; John J. Slattery, Harding, Mass.; George S. Sprague, White Plains, N. Y.; Samuel Tartakoff, Boston.

In Psychiatry: Frederick H. Allen, Philadelphia; Richard Francis Binzley, Brentwood, N. Y.; Daniel Blain, New York; James Arnold Brussel, Brentwood, N. Y.; Noble R. Chambers, Syracuse, N. Y.; Benjamin Cohen, North Grafton, Mass.; Roger Cohen, Washington, D. C.; Olive Alfreda Cooper, Boston; Kenneth Matthew Corrin, Wernersville, Pa.; Lee Wallingford Darrah, East Gardner, Mass.; Eugene Davidoff, Syracuse, N. Y.; Helen Flanders Dunbar, New York; Oliver Spurgeon English, Philadelphia; Robert Edward Fleming, Boston; Bardwell Hastings Flower, North Grafton, Mass.; William Charles Gaebler, Foxboro, Mass.; Rafael Hernandez, Nashville, Tenn.; Harold D. Palmer, Philadelphia; Francis Paul, Greens Farms, Conn.; Guy Charles Randall, Northampton, Mass.; Leonard Rosenzweig, Warren, Pa.; Leon Joseph Saul, Chicago; Francis Harper Sleeper, Worcester, Mass.; Lauren Howe Smith, Philadelphia; Annette Clarke Washburne, Madison, Wis.; Paul White, Dallas, Texas; John C. Whitehorn, Waverley, Mass.; Charles Simpson Woodall, Waverley, Mass.

In Neurology: Madelaine Ray Brown, Boston.

*Without Examination.*—Neurology and Psychiatry: Charles Sidney Bluemel, Denver; Eugene Feilen Bogen, Danville, Ill.; William Edler, Pasadena, Calif.; Walter C. Haviland, Middletown, Conn.; George Alexander Johns, St. Louis; Louis J. Karnosh, Cleveland; Fritz H. Lewy, Philadelphia; John McDowell McKinney, New York; John J. O'Donnell, Erie, Pa.; Elias Alfred Reed, Brooklyn; Henry A. Reye, Detroit; William W. Richardson, Mercer, Pa.; Henry Mason Smith, Tampa, Fla.; Meyer Solomon, Chicago; Theodore T. Stone, Chicago; Charles W. Thompson, Pasadena, Calif.; Charles Frederick Williams, Columbia, S. C.; David C. Wilson, University, Va.; Andrew Henry Woods, Iowa City; Joseph C. Yaskin, Philadelphia; Philip Work, Denver.

In Psychiatry: Frank Haslehurst Barnes, Stamford, Conn.; Earl Danford Bond, Philadelphia; James E. Boone, Columbia, S. C.; Emory John Brady, Colorado Springs, Colo.; Sidney Moore Bunker, Westwood, Mass.; Ross McClure Chapman, Towson, Md.; Russell Comber Doolittle, Des Moines, Iowa; Phyllis Greenacre, New York; Percy Gatling Hamlin, Newport News, Va.; Thomas J. Heldt, Detroit; Henry I. Klopp, Allentown, Pa.; Clinton Preston McCord, Albany, N. Y.; Karl A. Menninger, Topeka, Kan.; Clarence Paul Oberndorf, New York; Mable D. Ordway, Boston; Charles F. Read, Elgin, Ill.; Clarence J. Slocum, New York.

In Neurology: Fred Plumer Currier, Grand Rapids, Mich.; William Gordon Lennox, Boston; Russell Galbraith MacRobert, New York; Ernest Spiegel, Philadelphia.

## THE GEORGETOWN UNIVERSITY BRAIN RESEARCH INSTITUTE

On September 10 the Georgetown University School of Medicine, Washington, D. C., established an institute for the investigative study of the brain. This institute will be known as the Georgetown University Brain Research Institute and will be under the direction of Dr. Othmar Solnitzky, professor of anatomy, with Dr. Francis J. Warner as assistant director.

A comprehensive program of neurologic research work will be launched in the four following directions: (1) a complete study of the brains of vertebrates, from the cyclostomes to the primates; (2) a thorough study of the development of the human brain, with special regard to its morphology, nuclear masses and fiber tracts; (3) an experimental study of the function of the various nuclei and fiber tracts of the brain by means of Marchi degeneration and retrograde cell degeneration, and (4) a comprehensive study of the neuropathology of the human brain.

The institute already possesses a large collection of animal and human brains, many of which are sectioned and stained. The instrumentarium will include, among others, the Horsley-Clarke stereotaxic instrument, the Vogt-Sartorius brain microtome, celloidin and paraffin microtomes, a specially constructed brain macrotome, cold electric cautery, moving-picture camera, photomicrographic camera and dissection microscopes. The institute will also have two full time, specially trained technicians, a photographer and an artist. A large library of books, monographs and reprints covering every phase of the projected research is available. A modern and well equipped laboratory for animal experimentation is being built.

The facilities of the institute will be made available to all interested in any phase of brain research. Individual desks and microscopes will be placed at the disposal of investigators.

Contributions of animal and human brains, both normal and pathologic, as well as reprints of all neurologic publications, will be gratefully accepted and duly accredited.

## APPOINTMENTS TO FELLOWSHIPS 1937-1938

Under a grant from the Commonwealth Fund, the National Committee for Mental Hygiene has made the following appointments for one year's training in extramural psychiatry: at the Judge Baker Guidance Center, Boston, Dr. Reynold A. Jensen, a graduate of the University of Minnesota Medical School, with one year each at the psychiatric department of the Strong Memorial Hospital, Rochester, N. Y., and the Pennsylvania Hospital, Philadelphia; at the Mental Hygiene Clinic, Louisville, Ky., Dr. Edward Everett Landis, who obtained his medical degree from Northwestern University Medical School and comes to this fellowship from the State Hospital, Fulton, Mo. At the Child Guidance Clinic, Cleveland, Dr. Joseph C. E. LaVallee, who obtained his medical degree at Syracuse University College of Medicine in 1926 and has recently been resident psychiatrist at the Buffalo City Hospital, and at the Philadelphia Child Guidance Clinic, Dr. Robert Penn Kemble, who graduated from Jefferson Medical College of Philadelphia in 1933 and has served a residency at the Pennsylvania Hospital and the Payne Whitney Psychiatric Clinic, New York Hospital.

## OPPORTUNITIES FOR FELLOWSHIPS

A limited number of fellowships have been provided by the Commonwealth Fund and other sources for training in extramural psychiatry. These fellowships are to be administered by the National Committee for Mental Hygiene, through whom fellows are to be assigned for one or two years to a selected child guidance

clinic, the term and plan of the fellowship to be determined by the peculiar needs of the fellows. Candidates for award of fellowships should have had at least two years of psychiatry in an approved hospital for mental diseases, in addition to other qualities fitting them for extramural service. This provision for training fellowships comes in response to a definite paucity of personnel in this field. Accordingly, other conditions, such as age, sex and marital status, must be governed by the nature of the individual case and the current demand. Requests for further information about these fellowships, and applications therefor, should be addressed to Dr. George S. Stevenson, the National Committee for Mental Hygiene, Room 822, 50 West Fiftieth Street, New York.

## RESIDENCIES IN NEUROPSYCHIATRY

Four residencies per year for the Menninger Sanitarium, Topeka, Kan., have been approved by the Council on Medical Education and Hospitals of the American Medical Association. Periods of residency now begin on January 1, April 1, July 1 and October 1. The candidate for appointment on Jan. 1, 1938, will be chosen October 1; all applications must have been received by September 1 so that the credentials and references can be investigated prior to appointment of the resident. Minimum requirements for candidacy are graduation from an approved medical school and completion of an internship in an approved hospital. The salary for residents is $120 a month without maintenance.

Didactic instruction is arranged with the staff members, and the residents are eligible to attend seminar discussion groups, staff conferences, sessions of the postgraduate courses for nurses and for physicians and class work in neurology, neuropathology, psychiatry and psychoanalysis.

Application blanks will be mailed on request. Address: Dr. Karl A. Menninger, Chief of Staff, The Menninger Clinic, Topeka, Kan.

## SAINT ELIZABETHS HOSPITAL, WASHINGTON, D. C.

Dr. Winfred Overholser, until recently commissioner of the Department of Mental Diseases, State of Massachusetts, has been appointed superintendent of Saint Elizabeths Hospital by President Roosevelt, to succeed the late Dr. William A. White.

## MEDICAL SOCIETY OF ST. ELIZABETHS HOSPITAL WASHINGTON, D. C.

A society was recently organized in Washington, D. C., by a number of the present and former members of the medical staff of St. Elizabeths Hospital. It is planned as an alumni society of the hospital, to include physicians now serving, or having served, at the hospital. In general, it will sponsor and support efforts tending to promote the best interests of the hospital and will serve to maintain among its members pleasant associations with the hospital and with each other. The encouragement of a program of guided psychiatric research at the hospital is a contemplated feature of its program.

Officers elected at the initial meeting are: Dr. Addison M. Duval, president; Dr. Joseph L. Gilbert, vice president, and Dr. Jay L. Hoffman, secretary.

Communications from former members of the staff (including medical officers in the military services who have been assigned to the hospital) are invited and should be addressed to the Secretary, Medical Society of St. Elizabeths Hospital, St. Elizabeths Hospital, Washington, D. C.

# Abstracts from Current Literature

## Anatomy and Embryology

THE DEVELOPMENTAL PATTERN OF ECTODERMAL PLACODES IN RANA PIPIENS. RALPH A. KNOUFF, J. Comp. Neurol. **62**:17 (Aug.) 1935.

For this study three series of embryos of Rana pipiens were available. The most significant morphologic events in the development of the placodal system occur during the period extending from the early neural plate stage to the 5 mm. stage. Eight critical stages within this period are described and illustrated. Functionally, specific ectodermal placodes in Rana pipiens were observed to emerge from a common primordium, which has the form of a continuous longitudinal thickening of the ectoderm. This primitive placodal thickening is broad and relatively deep in the anterior head region and becomes progressively narrower posteriorly. It consists of a simple or pseudostratified layer of tall columnar, heavily pigmented cells immediately adjacent to the neural plate. The rostral portion continues to develop and differentiates into the hypophysis and olfactory placodes and furnishes the ectoderm which lines the stomodeal cavity.

FRASER, Philadelphia.

THE INTRAMEDULLARY COURSE OF THE DORSAL ROOT FIBERS OF EACH OF THE FIRST FOUR CERVICAL NERVES. KENDALL B. CORBIN and JOSEPH C. HINSEY, J. Comp. Neurol. **63**:119 (Dec.) 1935.

This study was made from serially sectioned material stained with the Marchi technic, obtained from the cervical portion of the cord and the medulla of nineteen cats on which various operative procedures had been carried out. These were: removal of the first cervical dorsal root ganglion unilaterally, the second unilaterally, the third unilaterally, the fourth unilaterally, the first and second unilaterally and the first bilaterally, and section of the right first and the left fourth cervical dorsal root and of the right second and the left fourth cervical dorsal root.

The descending fibers from any root could never be followed for more than two segments below their entrance into the cord. The ascending fibers from the fourth cervical dorsal root form a narrow strand in the fasciculus cuneatus, extending from the periphery of the cord, from a point about 0.5 mm. dorsomedial to the fasciculus gracilis, running in a broad curve toward the border of the central gray matter terminating from 1 to 2 mm. dorsolateral to the central canal. Between this band of ascending fibers and the posterior horn of gray matter are situated the ascending fibers of the first three cervical dorsal roots. A large number of fibers from the dorsal root pass into the central gray matter at the level of the entrances of the roots. These medially directed fibers appear to terminate for the most part about the intermediate nucleus of Cajal; a few are distributed to the nucleus of the tractus solitarius, to the uncinate fasciculus and to the caudal portion of the descending vestibular root. A few pass into the anterior horn, and a still smaller number may be seen crossing in the posterior gray commissure. Ascending branches of the individual upper four cervical dorsal roots are situated dorsomedially to the spinal tract of the fifth nerve and maintain the same relative position seen in the upper cervical portion of the spinal cord. The ascending bundle of each root gradually diminishes in size as it reaches the points of exit of the vagus rootlets.

ADDISON, Philadelphia.

THE EFFERENT FIBERS OF THE FRONTAL LOBE OF THE MONKEY, MACACA MULATTA. PAUL M. LEVIN, J. Comp. Neurol. **63**:369 (April) 1936.

Fourteen young adult rhesus monkeys were used for this study. Lesions were made in the cortex of the entire frontal lobe or in various portions of it. The

margins of the lesions always lay well within the boundaries of the cyto-architectural areas. In some cases these boundaries were mapped out electrically. After fourteen days the brain and the spinal cord were treated by the Marchi method.

The anterior limb and genu of the internal capsule are composed of fine fibers from the prefrontal region. Medium-sized fibers from area 8 form a fairly compact bundle and lie in the anterior extremity of the posterior limb, close to the genu. Behind these are the fibers from area 6 and then those from area 4. The premotor and motor fibers are largely, but not entirely, intermingled. The posterior one third of the posterior limb does not degenerate after destruction of the cortex of the frontal lobe. The cerebral peduncle is the direct continuation of the genu and the posterior limb of the internal capsule. At its inner margin lie the fibers of the genu, derived from the prefrontal region. Lateral to and partly mixed with these fibers is the bundle from area 8. Fibers originating from area 6 occupy the medial three fifths of the peduncle, except for its most medial margin. Fibers from area 4 occupy the middle two-thirds, being intermingled partly with those from area 6. The lateral one-fourth is free from degeneration after lesion of the frontal lobe. An extensive prefrontal-thalamic system appears to arise mainly from the convexity of the frontal lobe, area 9. The other descending fibers to the midbrain and the pons seem to arise from the anterior portion of the inferior frontal gyrus. No degeneration of fibers is to be seen in the substance of the caudate nucleus itself, but this may be because this nucleus contains few and thin myelinated fibers. Definite degeneration in fibers of the globus pallidus was seen only in the experiment in which the entire cortex of the frontal lobe was damaged. It is evident that certain differences exist in the terminations of the projection systems from the various cyto-architectural areas of the frontal lobe. Thus, it is seen that from both the motor and the premotor area numerous fibers descend and terminate in various subcortical nuclei, chiefly the substantia nigra and the pontile nuclei. The important difference between the projection systems of these two areas is the presence of the great corticospinal tract in the projection system from the motor area. The cyto-architectural difference in these areas lies in the presence of gigantopyramidal cells in the motor area.

In this report Levin studied the projection fibers from the frontal lobe in a large number of animals and expanded the work of Mettler on the corticifugal fiber connections of the frontal lobe observed in five animals. Levin shows restraint in his conclusions but emphasizes that a pattern exists in the relationship of the various cellular areas of the frontal lobe and the terminations of the projection systems, namely, that the more anterior regions are connected predominantly with higher subcortical structures and the more posterior with lower subcortical structures. The prefrontal region sends its efferent fibers predominantly to the rostral portion of the thalamus, and the premotor area, to the midbrain and pons. The motor area sends a great fiber tract also to the spinal cord.

FRASER, Philadelphia.

THE INNERVATION OF THE MUSCLE OF ACCOMMODATION IN THE EYE OF THE TELEOST, HOLOCENTRUS. RALPH G. MEADER, J. Morphol. **59**:163 (March) 1936.

The resting teleost eye is accommodated for near vision. Active accommodation for distant vision is secured by movement of the lens toward the retina, effected by contraction of the retractor lentis (campanula Halleri) muscle. Anatomic study of the large-eyed nocturnal squirrel-fish, Holocentrus ascensionis (Osbeck), showed that this muscle derives its innervation from the ciliary ganglion, by way of a ramus of the short ciliary nerve. This ramus traverses the vitreous humor in an invaginated fold of choroid, the processus falciformis. It is composed chiefly of heavily myelinated fibers, with a few finely myelinated or unmyelinated fibers. The myelinated fibers are probably post-ganglionic motor fibers from the cells in the ciliary ganglion, sensory dendrites

of cells in the profundus ganglion and postganglionic fibers from the trigeminal sympathetic ganglion. The last-mentioned fibers, together with the finely myelinated and unmyelinated fibers, may innervate the accompanying blood vessels.

WYMAN, Boston.

EMBRYOLOGY OF THE NERVOUS SYSTEM IN THE GRASSHOPPER, MELANOPLUS DIFFERENTIALIS (ACRIDIDAE; ORTHOPTERA). VICTOR BADEN, J. Morphol. **60**:159 (Dec.) 1936.

Embryos of Melanoplus differentialis were fixed and sectioned, and the development of the nervous system was traced by the fourteen stages illustrated in plates 1 and 2 of O. E. Nelsen (The Segregation of the Germ Cells in the Grasshopper, *J. Morphol.* **55**:545, 1934). The development was observed to be similar in general to that already described for other insects. Terms such as "ganglionic gangliomeres," "medullary masses" and "optic nerve" were proved to have no significance, and the "intraganglionic thickening" of Viallanes was shown to be a misnomer. The development of the nervous system is described in detail, and a chronological table giving the extent of the development for each stage in the embryologic history of the grasshopper is presented.

WYMAN, Boston.

CELL DIVISION AND DIFFERENTIATION IN THE GROWTH OF SPECIALIZED VERTEBRATE TISSUES. ARTHUR COHEN and N. J. BERRILL, J. Morphol. **60**:243 (Dec.) 1936.

The postembryonic growth of the notochord, sensory retinal cells, cartilage and gut was studied in frog tadpoles, recently hatched trout (Salvelinus fontinalis) and lamprey larvae (Petromyzon fluviatilis). Increase in the number of notochordal and sensory retinal cells results only from mitotic division of cells which have not yet undergone the structural modifications characteristic of these cells. The specialized and functional cell does not divide. Cartilage and gut epithelium grow, however, by mitotic division of fully formed and functional cells. This ability is believed to be due to their structural simplicity, which presents no mechanical difficulties for division. The sensory cells of the retina and the vacuolated cells of the notochord, on the other hand, are much modified structurally, and irreversibility of these modifications is believed to preclude the possibility of division. Growth, therefore, results only from the division of simple and as yet unmodified cells.

WYMAN, Boston.

THE ORIGIN OF THE POSTERIOR CEREBRAL ARTERY. D. J. WILLIAMS, Brain **59**: 175, 1936.

After studying the perivascular innervation of cerebral vessels, Williams asserts that the posterior cerebral artery is morphologically a terminal branch of the internal carotid artery. This conclusion was reached after a study of the great vessels comprising the circle of Willis and its main branches in normal adult human brains. Abbie (1933 and 1934) recently described the comparative anatomic structure of the posterior cerebral artery. He showed that in amphibia (Rana) this artery develops from the hippocampal artery of the lower forms. In reptiles (Sphenodon) it is mainly the hippocampal artery which has acquired a nearer source of origin for its blood, by means of a more posterior anastomosis with the cranial division of the internal carotid artery. In mammalia (Ovis) he observed that the posterior communicating artery is larger than the posterior cerebral artery. In subprimates the posterior communicating artery runs from the internal carotid artery to the basilar artery and is clearly the caudal division of the internal carotid artery. In primates the change is complete; in man, except when developmental anomalies occur, the posterior cerebral arteries are apparently the terminal branches of the basilar artery.

Wide anatomic variations in the posterior communicating artery have been described. Stopford (1915) observed that it is larger than the posterior cerebral

artery on both sides in 2 per cent of cases in which he made examination, and larger on one side in 4 per cent. Fawcett and Blachford (1906) noted absence of the posterior communicating artery in 1.8 per cent of cases on the right side and in 1.4 per cent on the left. In these cases the posterior cerebral artery arose directly from the internal carotid artery. Abbie has described wide variations in anastomosis between the anterior choroid, the posterior communicating and the posterior cerebral artery.

In the present investigation, examination of the cerebral arterial tree in four early fetuses disclosed that in all the posterior communicating artery was relatively larger and thicker than in the adult and that its lumen was relatively wider. Stopford stated that the importance of the posterior communicating artery is much greater in intra-uterine life, when it represents the origin of the posterior cerebral artery from the internal carotid artery.

Shellshear (1920) postulated that the distribution of arteries obeys some otogenic and phylogenetic law. He said that the evolution of the vessels is dependent on, and proceeds hand in hand with, the evolution of their fields of distribution. Thus, the arteries of the brain, being as much a part of the neurovascular mechanism as the brain itself, have shown changes concurrent with the more specialized development of the central nervous system. As the brain has expanded to meet new and increasing requirements, its arteries have extended to satisfy the increased functional demands. In the backward growth of the cerebral hemispheres over the midbrain, the distribution of the posterior cerebral artery has been separated further and further from the parent trunk, the internal carotid artery. In accordance with natural economy, a nearer course of supply has been found in the anastomosis of the basilar artery with the posterior cerebral artery. Concomitant with the increasing functional demands of the posterior cerebral artery, the basilar artery has enlarged adequately to supply the increasing amount of cerebral tissue. Although functionally the posterior cerebral artery is a terminal branch of the basilar artery, morphologically it is one of the three terminal branches of the internal carotid artery. The carotid system is therefore distributed to the whole of the forebrain and midbrain, while the phylogenetically older vertebral system is confined strictly to the hindbrain.

Thus, all the evidence produced confirms the view that the posterior cerebral artery is morphologically a terminal branch of the internal carotid artery.

SALL, Philadelphia.

INNERVATION OF THE SWEAT GLANDS. K. KURÉ, S. OKINAKA, S. MAÉDA and H. KATO, Arch. f. d. ges. Physiol. **237**:40, 1936.

On the basis of studies on cats, three types of innervation of the sweat glands are distinguished: 1. Sympathetic Innervation: The centers for the sweat glands of the forepaw are located in the middle thoracic segments, and those for the hindpaw, in the lower thoracic and upper lumbar segments. The efferent fibers pass through the anterior roots and the sympathetic chain; they react to drugs like parasympathetic fibers. Their centers are stimulated by application of heat. 2. Sacral-Parasympathetic Innervation: These fibers make their way through the anterior roots to the sweat glands of the hindpaw without relation to the sympathetic chain. The centers for these fibers are not stimulated by application of heat. 3. Spinal-Parasympathetic Innervation (efferent fibers in the posterior roots): The fibers to the hindpaw have centers in the sixth and the seventh lumbar and the first sacral segment; they reach the glands partly directly and partly through the sympathetic chain. The fibers for the forepaw center in the eighth cervical and the first and second thoracic segments; they pass directly to the glands of the forepaw, at least partly; the indirect pathway through the sympathetic chain has not been shown as yet. The whole body of the cat has at least rudimentary sweat glands with a segmental parasympathetic innervation. Only fibers that pass through the sympathetic chain are stimulated by heat and by pilocarpine.

SPIEGEL, Philadelphia.

RELATIONSHIP OF MICROGLIA CELLS TO THE BLOOD VESSELS. ENRIQUE VÁZQUEZ-LÓPEZ, Arch. f. Psychiat. **104**:652 (March) 1936.

Vázquez-López discusses the problem of the origin and nature of the Hortega cells and their relationship to the blood vessels. He describes a series of investigations on the brain and spinal cord of hens from 2 to 5 months of age. Most of these animals were healthy, but some suffered from Rous sarcoma. In a few cases there were metastases of the sarcoma in the brain tissue. In the normal mature hen the microglia cells present certain characteristics which are not observed in man. The most important differences are: 1. A great variety of different stages of development of the microglia cell, ranging from the early microgliablast to the adult, well developed cell. In the healthy fowl these stages do not present any pathologic features, such as gitter cells. The early forms are in a constant state of mobilization, apparently ready to move to any point where injury or infection exists. 2. Throughout the central nervous system, especially in the white matter and particularly in that of the cord, there are occasional colonies of microglia cells grouped around small vessels or capillaries. The cells are thickly crowded in the center of such a colony and represent immature types, some of them bearing a striking resemblance to cells of blood vessels and others to pericytes. As one nears the periphery, the cells become less thickly congested and more mature, until at the very periphery one comes to isolated cells of a nearly mature form. These colonies are regarded as replacement stations from which microglia cells can be transported to points where they are needed. Actually, in case of metastatic growths in the central nervous system, these colonies seem to be depleted gradually as the microglia cells are detached and displaced to the site of the lesion. Vázquez-López considers these facts as significant in indicating the mesodermal rather than the ectodermal origin of microglia cells.

MALAMUD, Iowa City.

A THIRD ARTERY OF THE RED NUCLEUS. KARL STERN, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:519 (April) 1935.

There are two blood vessels known as the arteries of the nucleus ruber. One arises almost in the median line from the posterior cerebral artery on either side, coursing directly to the nucleus of the third nerve and sending a branch to the nucleus ruber. Occlusion of this branch results in the syndrome of Claude, sometimes known as the rubro-oculomotor or inferior syndrome of the red nucleus. The other artery is more cephalad. It also arises near the median line from the posterior cerebral arteries. It ends in the central gray matter in that part of the thalamus nearest the ventricle and gives off a branch to the red nucleus. Occlusion of this vessel results in the syndrome of Marie and Guillain, which is also known as the rubrothalamic syndrome as well as the superior syndrome of the red nucleus.

Stern describes a third vessel to the red nucleus, hitherto not mentioned in the literature. This vessel was found in about half of the brains studied. It is an isolated, small vessel which arises either from the posterior cerebral or more rarely from the superior cerebellar artery, away from the midline, as these vessels wind around the pes pedunculi. The vessel passes through the basis pedunculi and the substantia nigra and enters the nucleus ruber ventrally. Occasionally the vessel gives off a small branch which supplies an area just ventral to the red nucleus. There is no reported case of softening in the area supplied by this vessel. In cases of thrombosis of the superior cerebellar artery described by Critchley, in which the red nucleus was involved, the condition was probably due to occlusion of this third artery of the red nucleus when it arose from the superior cerebellar artery.

SAVITSKY, New York.

ONTOGENESIS OF THE ISOCORTEX IN MAN. G. I. POLIAKOV, Trudy inst. mozga **2**:9, 1936.

Poliakov studied the early ontogenesis of the isocortical formations in man. He describes the organization of the lamina corticalis in a 13 week human embryo, 90 mm. long. He observed that the development of the lamina corticalis takes place more intensively in the central part of the hemisphere, diminishing gradually in all directions toward the periphery. He describes several phases in the development of the lamina corticalis, involving mainly changes in the intensity of the migration rate of the neuroblasts from the matrix to the lamina corticalis: (1) primary separation of the lamina corticalis, which he defines as the type A formation; (2) primary consolidation of the lamina corticalis, which he calls the type B formation; (3) primary differentiation of the completed consolidation in the stratum superficiale, which is narrow and condensed, and in the stratum profundum, which is wide and friable—type C formation; (4) secondary consolidation of the lamina corticalis, with thickening and enlargement of the stratum superficiale at the expense of the stratum profundum and disappearance of the differentiation into layers—type D formation, and (5) secondary differentiation of the consolidated parts. This differentiation results finally in the division of the cortex into the layers of the adult brain and is the type E formation. Poliakov states that the development of the lamina corticalis does not pass successively from one phase to another over the entire surface of the hemisphere. In each embryonal stage the lamina corticalis presents different types of formation in different regions. The distribution of the various types of formations on the surface of the hemisphere and the consecutiveness of replacement of the various types in different regions depend apparently on the principle of radiation. As a result of this tendency, the more centrally located part of the lamina corticalis reveals an advanced type of formation, as compared with the peripheral regions. Formation of the lamina corticalis seems to take place from neuroblasts and is influenced by the development of nerve fibers. This may explain certain peculiarities in the formation of the stratum profundum in the type C formation, which is characterized by an undular distribution of the neuroblasts in the frontal lobe.

NOTKIN, Poughkeepsie, N. Y.

## Physiology and Biochemistry

THE CHANGES IN THE CELLS OF THE STRIATED DUCTS OF THE CAT'S SUBMAXILLARY GLAND AFTER AUTONOMIC STIMULATION AND NERVE SECTION. H. E. RAWLINSON, Anat. Rec. **63**:295 (Oct. 25) 1935.

Sympathetic and parasympathetic stimulation causes histologic changes in the striated duct cells of the cat's submaxillary gland that can be interpreted as evidences of secretory activity. In recovery experiments in which the nerves to the gland were sectioned, there were also changes in the ducts. In considering the nature of the control over the secretory activity of these ducts, the factor of changes in the blood flow is stressed, but there is evidence that vasodilatation per se does not cause secretion.

COBB, Boston.

THE SIGNIFICANCE OF THE DIFFERENT TYPES OF CELLS OF THE ANTERIOR PITUITARY. W. SUSMAN, Endocrinology **19**:592 (Sept.-Oct.) 1935.

There is some question whether the various types of cells in the anterior lobe of the pituitary gland are separate varieties or merely different phases of one type of cell. The technic of Susman's study was as follows: Material was obtained from a series of 255 unselected autopsies. Each gland was divided through the center, anteroposteriorly. The sections were stained by one or several of the following methods: (1) hemalum and eosin, (2) Weigert's iron hematoxylin and eosin and (3) acid fuchsin and methyl green. Two thousand consecutive cases in which necropsy was performed served as controls. Data were compiled as to

age and sex. The method for estimating the proportion of the various types of cells present was: The whole cell content of the anterior lobe of the pituitary was given the maximum value of 10; the cell type that was least numerous was then examined, and if these cells were present to the extent of only a scattering, this type was given the value of 1; if, however, the cells were more plentiful and yet not numerous, the numerical value was 2; if this type was numerous but not abundant, the value was 3; if the cells were abundant, the reading was 4, and so on. Thus, it is obvious that after two readings had been obtained, the remaining reading could be made through simple subtraction. Usually this result was checked by a third reading. Susman concludes, after detailed examination of 255 glands, that the basophilic, acidophilic and chromophobic cells in the anterior lobe of the pituitary are phases of one type of cell. This conclusion is at variance with that of Cushing, who proposed the theory that each cell represents a distinct type and each is responsible for a distinct secretion. In addition, the data disclosed that the pituitary gland responds to the demands of general diseases in one of two ways: An increased demand for the growth hormone gives rise to an increase in the number of acidophilic cells, representing an increase in the normal activity of the gland, or an emergency function comes into play when the subject has been exposed to shock. Then the acidophilic content of the anterior lobe of the pituitary is emptied, and the cellular exhaustion shows itself by an increase in the number of chromophobic cells. Thus, the pituitary gland has a normal function, namely, the control of cell growth, and an emergency function, best seen in connection with shock.

PALMER, Philadelphia.

THE CARBOHYDRATE METABOLISM OF BRAIN: I. THE DETERMINATION OF GLYCOGEN IN NERVE TISSUE. STANLEY E. KERR, J. Biol. Chem. **116**:1, 1936.

A modification of the Pflüger procedure is presented for determining the amount of glycogen in the brain. The essential points of modification are: (*a*) avoidance of postmortem change in preparing the tissue for analysis; (*b*) rapid solution of the tissue by digestion with a hot alcoholic solution of potassium hydroxide; (*c*) separation of cerebrosides by means of a mixture of hot methyl alcohol and chloroform, and (*d*) correction for nonfermentable reducing substances liberated during acid hydrolysis. By this method the recovery of glycogen added to brain averaged 95.6 per cent. Values from 70 to 130 mg. per hundred grams are found in mammalian brain frozen in situ.

PAGE, New York.

ACTION POTENTIALS IN THE NERVOUS SYSTEM OF THE CRAYFISH: V. TEMPORAL RELATIONS IN PRESYNAPTIC AND POSTSYNAPTIC RESPONSES. C. LADD PROSSER, J. Cell. & Comp. Physiol. **7**:95 (Oct.) 1935.

The conduction velocities of responses in the ventral nerve cord of the crayfish to proprioceptive stimulation range from 3 to 10 meters per second, and ganglionic delays are from 3.5 to 4.5 milliseconds. Delays are longer in the sixth abdominal ganglion. A few fibers pass without synaptic delay through each ganglion except the sixth abdominal ganglion. Afferent responses set up by stimulation of caudal sensory hairs give evidence for an excitation time of from 0.5 to 1.5 milliseconds at the receptors. The afferent response adapts at a steady rate during repetitive stimulation and fails to synchronize with repetitive stimuli of frequencies above 100 per second. The nonfunctional period of recovery for the afferent response in 30 per cent of the fibers is of the order of from 5 to 10 milliseconds and is less than 5 milliseconds in the remainder. The periods of relative recovery last until approximately 10 milliseconds after stimulation. Anterior to the caudal ganglion, the efferent response shows a ganglionic delay of from 5 to 7.5 milliseconds. This response equilibrates rapidly and fails to synchronize with repetitive stimuli faster than 10 per second. A nonfunctional period of recovery of approximately 0.1 second, but no period of relative recovery, is observed for the efferent response in single fibers.

Prosser considers that excitation time is correlated with attenuation of fibers, that adaptation and equilibration may be due to a similar mechanism and that a period of relative recovery in an integrated response from a center measures the recovery of the discharging units in the center from an absolutely unrecovered state.

CHORNYAK, Boston.

THE PITUITARY-HYPOTHALAMIC MECHANISM; EXPERIMENTAL OCCLUSION OF THE PITUITARY STALK. W. MAHONEY and D. SHEEHAN, Brain **59**:61, 1936.

This study was carried out on twenty dogs and twenty monkeys. In every instance a silver clip was closed tightly about the pituitary stalk, as far distad from the tuber cinereum as possible. The animals were killed at periods ranging from three days to ten months after operation.

Occlusion of the pituitary stalk in monkeys did not result in polyuria or polydipsia. There was no significant alteration in the basal metabolic rate, the sugar level of the blood or the nitrogen and base constituents of the urine. In two animals, two weeks after occlusion of the pituitary stalk, a puncture was made in the tuber cinereum, which resulted in temporary polyuria and polydipsia, lasting three days and then rapidly returning to normal. Histologic studies disclosed no real change in the size or cyto-architecture of the glandular elements of the pituitary body.

In dogs occlusion of the pituitary stalk was invariably followed by extreme polyuria and polydipsia, which persisted for several weeks. In a few animals in which total thyroidectomy had been performed polyuria and polydipsia were abolished and could be reestablished by oral administration of desiccated whole thyroid gland. Occlusion of the pituitary stalk in immature dogs, from 6 to 7 weeks of age, was followed by the usual diabetes insipidus, but, in addition, there occurred marked retardation of growth and sexual infantilism, and subsequently extreme adiposity. Examination of the pituitary body in adult diabetic dogs disclosed a friable organ which, when ruptured, discharged a drop of oily brown fluid, leaving a collapsed cystic shell. Microscopically, the wall of the cyst consisted of necrotic cells of the pars distalis, with islets of cells remaining visible near the periphery, where the blood supply appeared to be adequate. Carmine-gelatin preparations showed almost complete avascularity of the tissues except in the peripheral part, where small blood vessels were to be seen. In some cases no pars nervosa tissue could be recognized, while in others portions of the pars nervosa showed no appreciable difference from that in preparations used as a control.

The histologic changes in the hypothalamus after occlusion of the pituitary stalk were similar in the dog and in the monkey. The nuclei of the cells of the supra-optic and paraventricular nuclei showed the characteristic eccentricity, but not the shrinkage and hyperchromatosis, diagnostic of retrograde cell change. No demonstrable changes were observed in the tuberal or mamillary nuclei.

In these experiments occlusion of the pituitary stalk in the monkey resulted in no clear physiologic evidence of failure of the pituitary hormones to reach the general circulation. This, with the complete absence of any histologic changes in the pituitary body in this animal, indicates that, in the monkey at least, the passage of secretion, if any, along the stalk is not of great significance. This does not disprove the theory that the pituitary principle acts on hypothalamic centers, for it may still do so by way of the general circulation.

The reasons for the difference in response of water metabolism in the dog and that in the monkey is not clear. The results can be explained in one of two ways. Diabetes insipidus may be attributed to lack of antidiuretic principle, due to degeneration of the pituitary of the dog. Such a view would be in accordance with all the histologic observations in the present study. Hypophysectomy, however, was not followed by diabetes insipidus in either the dog or the monkey, and in the latter, in the experience of Mahoney and Sheehan, hypothalamic lesions after preexisting hypophysectomy resulted in severe upset

of the water metabolism. Similarly, in the dog after hypophysectomy Camus and Roussy produced diabetes insipidus by a small lesion in the tuber cinereum. If, as Richter maintained (1934), the essential and only factor necessary for the production of diabetes insipidus is a lesion severing the connection between the "posterior lobe" and the nuclei of the brain stem, provided that some "anterior lobe" tissue remains, there is no clear explanation why the secondary lesions in the tuber cinereum after a preexisting hypophysectomy should be followed by polyuria. The fact that, in the monkey at least, the pars tuberalis spreads out under the tuber cinereum and is embedded in the substance of this part of the hypothalamus is of great importance in this problem, for complete hypophysectomy including the pars tuberalis is obviously impossible without destruction of the tuber cinereum.

Another explanation that may be offered for the difference in behavior in the exchange of fluids in the dog and in the monkey is that of injury to hypothalamic centers. There is an important anatomic difference in this region in the two species. In the dog the pituitary stalk is short and thick and contains a direct prolongation of the third ventricle, so that in this animal the stalk and the tuber cinereum are identical. In the monkey the stalk is a long, thread-like band connecting the clearly differentiated tuber with the pituitary body, and the relations are such that it is possible to place a silver clip around the stalk without injuring the adjacent structures. Furthermore, in this animal the third ventricle ends in the tuber cinereum proper and does not extend into the stalk. In the dog, therefore, the lower hypothalamic centers are damaged somewhat by the silver clip but are not involved in the monkey. Such an explanation would appear to fit all known facts, although it still leaves unexplained the antidiuretic action of a solution of posterior pituitary in experimental diabetes insipidus.

SALL, Philadelphia.

THE ANATOMICAL LOCALIZATION OF THE HYPOTHALAMIC CENTRE FOR THE REGULATION OF TEMPERATURE. C. H. FRAZIER, B. J. ALPERS and F. H. LEWY, Brain **59**:122, 1936.

It has been shown that the hypothalamus is important for the normal regulation of body temperature. Isenschmid and Krehl (1912) and Isenschmid and Schnitzler (1914) indicated that it is necessary to keep the hypothalamus intact in order to maintain normal body temperature, but they failed to specify the exact region of the hypothalamus necessary for this control. Bazett, Alpers and Erb (1933) attempted to locate more specifically the temperature-regulating area in the hypothalamus. They found in cats that the area in the walls and floor of the third ventricle is most essential for this function. This work was carried further by Alpers (1935), who studied two cases of tumor of the pituitary area in which death was accompanied by severe hyperthermia and loss of temperature control. In these cases the lesions were in the floor of the third ventricle, more particularly in the substantia grisea. The more lateral and dorsal portions of the hypothalamus were intact.

In this communication further experimental studies are recorded. They were undertaken to determine whether lesions placed in the substantia grisea, in the floor of the third ventricle, will produce loss of temperature control. Operation was performed on thirty cats, and bilateral lesions were placed mesially in the floor of the third ventricle by means of the Horsley-Clarke apparatus. In most animals the lesion was either too far lateral in the hypothalamus or was unilateral. In instances in which the lesions were properly placed, the loss of temperature regulation was complete. An excellent example of this was afforded by a cat that was completely thermolabile. At room temperature the rectal temperature was 24 C. In a room with a temperature of 32 C. the cat's temperature rose to 38 C.; it then fell to 34 C. during twenty minutes' exposure in a room at 2.5 C. The temperature of the cat continued to fall in the cold room, so that after five hours it was 15 C. There was no hyperpnea, no true panting and no evidence of shivering. Vasomotor responses in the foot-pads were lacking. Serial sections of the hypothalamic area revealed complete destruction of

the nucleus hypothalamicus anterior (Rioch), or the substantia grisea which lies in the floor of the third ventricle. The area destroyed extended from the anterior part of the optic chiasm to the infundibular region. Other hypothalamic nuclei including the nucleus paraventricularis, the nucleus supra-opticus, the nucleus lateralis hypothalami and the nucleus mamillaris, were all intact.

Laterally placed lesions, whether bilateral or unilateral, cause only transitory and fleeting disturbances in the regulation of temperature. It is the opinion of the authors that the lateral portion of the hypothalamic area is not essential for regulation of temperature.

Isenschmid and Krehl asserted that in the rabbit the most important area for the control of temperature is the tuber cinereum and that the region close to the third ventricle is of no greater importance for the regulation of temperature than areas more distant. The authors' observations are in disagreement with this and indicate that for complete loss of temperature control it is necessary to have bilateral destruction of the nucleus hypothalamicus anterior in cats and the substantia grisea in man.

SALL, Philadelphia.

CORTICAL SENSORY DISTURBANCES IN MAN. L. PINES, Encéphale **31**:357, 1936.

Cortical representation of sensory functions in man is complex, and the limits of its territory and the localization of the different forms of sensation are not yet well defined. Four cases are reported. In two no necropsy was performed, and in two histologic studies of the brain were made post mortem. In case 1 there were left hemianesthesia for superficial and deep sensation, continuous pain in the left extremities and left hemiparesis without exaggeration of the reflexes. The lesion proved to be a fresh hemorrhage which destroyed the entire posterior portion of the right lateral thalamic nucleus and touched the median center of Luys, without injuring any other portion of the thalamus or neighboring structures. An old malacic lesion was observed in the lenticula. There was degeneration in the two central gyri, particularly in the postcentral gyrus. Pines interprets this as ascending degeneration of thalamocortical fibers, which end not only in the postcentral but in the precentral gyrus. In case 2 there was diminished sensation to tactile, thermal and painful stimuli on the right side, with slightly spastic paresis on the same side. After jacksonian fits on the right there were asterognosis and atopomyognosis in the right hand. The Wassermann reaction of the blood was 3 plus. Necropsy showed a bronchial carcinoma with a metastatic tumor, "the size of a nut," in the cortex and subcortical tissue of the upper portion of the left precentral gyrus. The white matter of the precentral gyrus was almost entirely destroyed. The peripheral subcortical layer, containing the arciform fibers about the bottom of the central sulcus, was partially preserved. The conclusion from this case and from the preceding case is that the precentral gyrus has a sensory as well as a motor function. The opinion that the sensory and motor zones of the cortex are not distinct and that the sensory afferent fibers end in the regions giving rise to the motor efferent fibers was held by Dejerine, Exner, Horsley and other older authors. Since the work of Henschen, Long, Roussy, Sherrington and Grünbaum, the existence of distinct motor and sensory zones, the former in the precentral and the latter in the postcentral gyrus, has been generally agreed on, although the exact limits of the two zones have not been entirely worked out. Pines believes that while the precentral gyrus is principally motor, it is also the seat of an auxiliary sensory zone of projection, concerned with the forms of sensation which are necessary for the organization of a harmonized motor act. Two other cases of localized traumatic craniocerebral lesions, in which no autopsy was made, are described as examples of somatotopic localization of sensation and localization of sense qualities in the cortex. Thus, in one case there was diminution only of pain and thermal sensation, limited to the territory of the first sacral segment on one side. Pines assumes from the history and associated signs and symptoms that the lesions were exclusively cortical.

LIBER, New York.

CHANGES IN THE HYPOPHYSIS FOLLOWING A LESION IN THE INFUNDIBULAR SEX-REGULATING CENTER. M. CAHANE and TATIANA CAHANE, Rev. franç. d'endocrinol. **13**:366 (Oct.) 1935.

This article reports an experimental attempt to verify the existence of a center in the infundibular region destruction of which is thought to cause the adiposo-genital syndrome. Cahane and Cahane punctured the tuberoinfundibular region in fourteen rats. Six animals died; five survived but showed no particular symptoms, and the remaining three revealed interesting changes. One of the three animals died about fifteen days after the operation, being at that time in the second month of pregnancy. Autopsy revealed decomposed residuals in the cornua of the uterus. The second animal was killed six months and twenty days after the operation. Autopsy showed complete atrophy of one testis, while the other weighed only 0.32 Gm.; the size of the penis was reduced. The endocrine glands, including the hypophysis, showed no gross macroscopic changes. Histologic examination showed rarefaction of the glandular tissue, especially in certain parts of the anterior lobe of the hypophysis. The cytoplasm was greatly reduced; the number of cells in a field was on an average 50; the nuclei stained poorly, and numerous vacuoles were present. Some nuclei were deformed, and there was evidence of central chromatolysis. The third female animal was killed thirteen months after the operation, at which time there was an increase in weight of about 108 Gm. In spite of the presence of males in the cage, the animal did not become pregnant. Autopsy revealed pronounced atrophy of the genital apparatus, including the uterus and the ovaries, while the other endocrine glands showed nothing abnormal grossly. Histologically, the glandular tissue of the hypophysis was less compact; there was a reduction in the number of eosinophilic and cyanophilic cells, and the cellular protoplasm was reduced. The ovaries did not contain corpora lutea, and the tissue was rarefied. The thyroid gland appeared in a state of hyperfunction.

The experiments, according to the authors, tend to show that a lesion in the infundibular region causes atrophy of the genital apparatus and that these changes are probably brought about by the action of the hypophysis, which shows rarefaction of the glandular tissue, reduction of the mass of cytoplasm, decrease in the number of eosinophilic cells and nuclear changes.

NOTKIN, Poughkeepsie, N. Y.

EXPERIMENTAL EPILEPSY AND THE ENDOCRINE GLANDS. VITO LONGO, Neopsichiatria **1**:1, 1935.

Pancreatectomy abolishes and cortical application of insulin enhances the elicitability of convulsive seizures produced in dogs by Amantea's method of reflex stimulation (*Arch. f. d. ges. Physiol.* **188**:287, 1921).

ALEXANDER, Boston.

CIRCULATION IN THE LIVER ON STIMULATION OF THE SPLANCHNIC NERVE. P. ECKHARDT, Arch. f. d. ges. Physiol. **236**:361, 1935.

The circulation of the liver was studied in dogs and cats by introducing thermocouples into the portal vein and the abdominal and thoracic vena cava. Stimulation of the splanchnic nerve reduces the inflow of blood to the liver but increases the outflow from the liver into the vena cava. The liver plays the rôle of a reservoir for blood. Nerve impulses reaching the organ by the splanchnic nerve induce contraction of the liver. The result is an increased outflow of blood into the vena cava.

SPIEGEL, Philadelphia.

INFLUENCE OF THE SYMPATHETIC NERVE FIBERS ON THE CORONARY VESSELS. K. GOLLWITZER-MEIER and E. KRÜGER, Arch. f. d. ges. Physiol. **236**:594, 1935.

The circulation in the coronary arteries was measured in dogs by thermocouples, with the thorax closed. The experiments showed that there is a continuous sympathetic dilator innervation of the coronary arteries. The efferent

sympathetic fibers take origin from the eighth cervical to the sixth thoracic segment; they reach the cardiac plexus partly by passing through the stellate ganglion and partly by using direct fibers from the sympathetic chain. Some efferent postganglionic fibers leave the stellate ganglion in the ansa subclavia and from here reach the cardiac plexus. When the sympathetic chain was stimulated by currents of various frequencies, it was found that low frequencies induced only a rise of the general arterial pressure, while somewhat higher frequencies were necessary to induce dilatation of the coronary arteries. When the vagal constrictor innervation was paralyzed by atropine, the sympathetic dilator effect was more marked.

SPIEGEL, Philadelphia.

LOCAL NEUROGENOUS METABOLIC EFFECTS IN VASOCONSTRICTION OF CENTRAL ORIGIN. H. REIN and O. MERTENS, Arch. f. d. ges. Physiol. **237**:231, 1936.

Vasoconstriction due to stimulation of the vasomotor center in the medulla oblongata by carbon dioxide was studied in dogs under anesthesia induced with the sodium salt of secondary butylbetabromallylbarbituric acid (pernocton). The effect on the working muscle (electrically stimulated gastrocnemius muscle) was compared with that of clamping the femoral artery. The decrease in efficiency of the working muscle produced by clamping the artery is due to true fatigue. This is indicated by slow decrease in efficiency after clamping the artery and slow return of efficiency after removing the clamps. The effect of vasoconstriction induced by stimulation of the vasomotor center is different. The efficiency of the muscle drops simultaneously with the beginning of vasoconstriction and returns quickly to normal after vasoconstriction ceases; the anemia is not followed by reactive hyperemia. It is assumed that the central impulses induced by stimulation of the vasomotor center with carbon dioxide cause decrease of the muscular activity not merely by lowering the blood supply of the muscle but by inhibiting the production of energy in the muscle. Inhibition is also shown by decrease in the tonus of the muscle.

SPIEGEL, Philadelphia.

NEW PROBLEMS IN THE HUMOROPATHOLOGIC CHANGES IN THE CONVULSIVE STATES. F. W. KROLL, Arch. f. Psychiat. **104**:558 (Feb.) 1936.

Kroll reports a series of experiments in which extracts were made from the brain tissue of persons suffering from epileptic convulsions and from that of animals in which epileptiform convulsions were produced experimentally. The extracts were injected into a large number of animals (dogs and guinea-pigs) and the results noted. The author concludes: 1. Extracts from the brain tissue of an animal obtained during a convulsion are capable of producing convulsions in other animals. 2. The extracts contain a substance which is produced in the cortex, since extracts of other parts of the brain do not produce convulsions. 3. This substance is specific, since convulsive movements produced by stimulating the cortex yield a substance which causes similar types of convulsions, whereas convulsive movements produced by stimulating the spinal cord give rise to a substance which reproduces similar movements. 4. This substance, produced in the nervous system, enters the blood, and its presence in the blood can be demonstrated. Finally, Kroll believes that a relationship exists between this substance and the hormone that is thought to be produced by the brain.

MALAMUD, Iowa City.

## Neuropathology

THE PREVENTION OF NUTRITIONAL ENCEPHALOMALACIA IN CHICKS BY VEGETABLE OILS AND THEIR FRACTIONS. MARIANNE GOETTSCH and ALWIN M. PAPPENHEIMER, J. Biol. Chem. **114**:673, 1936.

A disorder occurring in young chicks kept on a synthetic diet is characterized by severe pathologic changes in the central nervous system. The disease, which has been named nutritional encephalomalacia, develops only during periods of active

brain growth. It is not infectious nor transmissible by inoculation. The disorder is rarely observed when the chicks consume a diet of natural foods. Goettsch and Pappenheimer found in vegetable oils a protective factor which is thermostable and resistant to aeration and ultraviolet irradiation. It can be extracted with ethyl alcohol and is present in the nonsaponifiable fraction.

PAGE, New York.

FAMILIAL SCHILDER'S DISEASE. A. MEYERS and T. TENNENT, Brain **59**:100, 1936.

Familial cases of Schilder's disease have been reported by Krabbe (1916), Scholz (1925) and Collier and Greenfield (1924). Meyers and Tennent report on an interesting family in which two brothers, aged 4 and 9 years, presented characteristic clinical findings and pictures of the disease at autopsy. The mother and father were alcoholic. There were three brothers. In the two cases of Schilder's disease there was an antecedent history of jaundice and severe gastro-intestinal symptoms. Two other children had had gastro-intestinal symptoms, but only one of them showed nervous symptoms, in the form of a slight degree of ataxia. The fifth child is normal in all respects at present. The mother, aged 37, at present shows evidence of a progressive spinal disorder suggesting disseminated sclerosis. Onset of her nervous symptoms followed that of the symptoms in her children.

Familial cases of Schilder's disease do not necessarily correspond closely in regard to pathologic changes. However, in the two cases reported the similarity in the distribution of the pathologic lesions is striking. The frontal lobes were preserved as a whole. The changes increased rapidly posteriorly until they involved all the white matter. The process was nearly symmetrical. In both cases there was preservation of the basal ganglia and cerebellum. In the affected areas there was severe infiltration of the vessels with plasma cells and lymphocytes, which penetrated into the parenchyma.

Meyers and Tennent suggest the possibility of an extracerebral factor as the cause of Schilder's disease (Ferraro, 1928, and Macnamara and Dickson, 1933). Greenfield (1933) had something similar in view when he suggested that in his cases of infantile progressive sclerosis there was a supply of abnormal lipoids. Globus (1932) expressed the belief that onset with gastro-intestinal symptoms is frequent in Schilder's disease. Gastro-intestinal disturbances not only preceded the neurologic symptoms in the two cases of Schilder's disease described by Meyers and Tennent but were recorded in the history of two other children in the family.

In both cases there was irregular demyelinization of the optic chiasm, extending to the optic nerves. In coronal sections in both cases, the peripheral and more particularly the ventral part of the optic tract was better preserved than the central and upper parts. Fat stains showed the process to be the same as that in the cerebral white matter. At the zone of demarcation was a layer of fat-laden globoid cells, indicating that the lesion was proceeding from the center toward the periphery. Monnier and Walthard (1934) described similar centrally placed lesions of the optic tract in a case of cerebral syphilis in which the anterior choroid artery supplying a part of the optic tract was obliterated. This may indicate a vascular origin of the changes in the optic tract in cases of Schilder's disease.

There was no systematic limitation of the lesion to functional units, although it is obvious that, according to the scheme of Brouwer and Zeeman (1923 and 1926), the papillomacular bundle must have suffered first and to the greatest degree. Equally interesting is the striking similarity of the lesions of the optic tract to those observed by Scherer (1932) in the well known disease in monkeys; the lack of peripheral optic lesions in Schilder's disease was one of the reasons that Schob (1931) and Spielmeyer (1931) did not accept a close relationship between these conditions. Furthermore, gastro-intestinal disturbances, so outstanding a feature in the disease in monkeys described by Schob and Scherer, are not foreign to Schilder's disease. The similarity applies to "honeycombed" lesions in the spinal cord of monkeys, which suggested to Scherer a condition related to

pernicious anemia. Honeycombed lesions occur in Schilder's disease (Wertham, 1932, and Marinesco, 1930), and they might be seen more frequently if more attention were paid.

Histologic similarities do not necessarily indicate a close etiologic relationship. Moreover, since Schilder's disease is not likely to be a disease entity, changes in one of its groups need not apply to another. The fact, however, that an apparently epidemic and transmissible disease (Gaertner, 1932 and 1933) and Schilder's disease of heredofamilial nature have much in common presents an interesting pathogenic problem requiring further attention.

SALL, Philadelphia.

INVESTIGATIONS ON THE PROBLEMS OF IMMUNITY AGAINST SPIROCHAETA PALLIDA IN GENERAL PARALYTICS TREATED WITH MALARIA. A. BECK, J. Ment. Sc. **82**:254 (May) 1936.

Improvement in cases of dementia paralytica after treatment with malaria is due to the disappearance of the spirochetes from the brain. The question remains as to what in malaria treatment causes this. At first it was thought that the high fever produced by malarial infection killed the spirochetes, but apparently this is not so, as improvement has been observed in cases in which the fever was mild. It is known that fever, no matter of what origin, causes an increase in normal and immune antibodies. A series of experiments was undertaken to determine whether an increase in syphilitic antibodies causes the cure.

Examinations were made of the behavior in vitro (immobilization and eventual agglutination) of Spirochaeta pallida in the presence of serum and cerebrospinal fluid from patients with dementia paralytica who had been treated with malaria. Examinations were also made in vivo for the existence of a bactericidal substance (spirochetocidin) and a phagocytosis-enhancing substance (spirochetotropin) in the serum and cerebrospinal fluid of patients with this disease.

The samples of blood and cerebrospinal fluid were taken from patients who had undergone treatment with malaria from two to six months before. Beck chose patients who had shown clinical improvement. Normal persons were used as controls to check the results.

All the experiments gave essentially negative results, thus presenting conclusive evidence that cure in dementia paralytica after treatment with malaria is not due to the presence of special immunologic bodies in the serum of patients with this disease. Beck concludes that the good results are due to the inflammatory reaction of the brain to the malaria. This is supported by the histologic evidence of other observers, who found an increase in the inflammatory reaction of the brain and in the aminonitrogen in the cerebrospinal fluid, pointing to increased destruction of cells. The exact mechanism of the inflammatory reaction of the brain and the mechanism by which the fight between the spirochetes and the cells takes place are still obscure.

KASANIN, Chicago.

BILATERAL ATROPHIC LOBAR SCLEROSIS FOLLOWING THROMBOSIS OF THE SUPERIOR LONGITUDINAL SINUS. R. M. NORMAN, J. Neurol. & Psychopath. **17**:135 (Oct.) 1936.

Atrophic lobar sclerosis comprises a number of degenerative diseases of the cerebral cortex which, although showing uniform morphologic features, differ in pathogenesis and etiology. A much discussed etiologic factor is that of birth injury; although there is evidence to support such a cause in some cases, the mechanism is not fully understood. It seems, however, that an intact vascular supply is important for the development of the cerebrum. In the analysis of such cases it is necessary to take into consideration probable prenatal influences, such as individual variations in angio-architecture. Norman stresses that a history of difficult labor does not alone indicate an ensuing cerebral trauma. Of greater importance is a history suggesting a cerebral vascular accident after birth. As an example of this, Norman reports the case of a child whose mother suffered during pregnancy from dermatitis, which was said to be due to streptococcic infection. The labor was "dry," but the child was delivered without forceps. He

was severely asphyxiated but was revived. On the second day after birth he had a sudden attack of respiratory distress, followed by somnolence. Subsequently, there developed gradually generalized spasticity of the extremities, convulsive seizures and mental retardation. The child died at the age of 5 years and 7 months, after a brief episode in which he was comatose. Necropsy revealed thrombosis of the superior longitudinal sinus in the parietal region. Immediately adjacent was circumscribed bilateral atrophy of the precentral and postcentral gyri and of the superior parietal lobe adjacent to the postcentral sulcus. The atrophy was more pronounced in the left hemisphere. Microscopically, the affected regions showed outspoken degeneration and loss of parenchyma, with gliomesodermal scar formation. There were similar but less pronounced changes in the white matter, thalamus and putamen and scattered foci in other parts of the cerebrum and cerebellum. In addition, there was demyelinization of the pyramidal tracts in the medulla and spinal cord, which could not be traced in regions above the medulla. Norman concludes that anatomically the lobar atrophy in the cerebrum was associated with thrombosis of the superior longitudinal sinus. He regards the changes in remote parts of the central nervous system as secondary to the primary cortical lesions. The degeneration of the pyramidal tracts apparently was not a simple descending demyelinization but conceivably was due to interruption of corticofugal impulses to the still imperfectly myelinated fibers. From a clinical standpoint, the history suggests an intracranial lesion sustained at birth, with subsequent extension of the damage on the second day after birth. The possibility of prenatal factors, such as developmental anomaly of the sinus and the effect of the streptococcic infection of the mother during pregnancy, in the production of such a focus is also discussed.

N. MALAMUD, Ann Arbor, Mich.

ANATOMIC AND CLINICAL STUDY OF A CASE OF FRIEDREICH'S DISEASE ASSOCIATED WITH MENTAL DISTURBANCES. J. O. TRELLES, Ann. méd.-psychol. **92**:760 (Dec.) 1934.

A complete histologic examination of sections of the nervous system of a patient with Friedreich's disease revealed, beside the classic medullary and submedullary changes, inflammatory lesions of the spinal ganglia and massive changes in the cerebellum.

MOORE, Boston.

PROBLEMS OF MULTIPLE GLIOMA. H. J. SCHERER, J. belge de neurol. et de psychiat. **35**:685 (Dec.) 1935.

Scherer does not believe that the occurrence of multiple glioma is rare, as in five of seventy cases of glioma in which autopsy was performed the tumor was multiple. Attention was first directed to this subject by Globus and Strauss who found six instances of multiple glioma in eighteen cases of glioblastoma multiforme. Cushing and Bailey found only two instances of multiple tumor in the great number of cases that they studied, but their statistics were derived mainly from surgical observations rather than from postmortem study.

The important question in this study, according to Scherer, is whether this tumor is definitely multiple and independent or whether it metastasizes from a single primary tumor. This problem will be solved only as knowledge of the etiology of glioma advances. The only glioma that is known to metastasize is the medulloblastoma. Among the concepts regarding the origin of glioma, the theory of embryonic malformation still predominates. This theory has been strengthened by the work of Bielschowsky and Globus on the relationship between glioma and tuberous sclerosis.

Five cases of multiple glioma are described. In none of them was there any resemblance to tuberous sclerosis, nor did any of the tumors have the characteristics of metastases. Although the cases studied did not aid in confirming his hypothesis, Scherer favors the view of Globus that multiple glioma originates in foci of tuberous sclerosis or, at least, that it arises as a form of dysembryoplasia. He does not believe, however, that the problem has yet been solved.

WAGGONER, Ann Arbor, Mich.

HISTOPATHOLOGIC ALTERATIONS IN A CASE OF BUCCOLINGUAL SPASM OF POSTENCEPHALITIC ORIGIN. V. DIMITRI, Rev. neurol. de Buenos Aires **1**:126 (Sept.) 1936.

Dimitri reports a case of contracture of the tongue associated with other abnormal movements of the mouth occurring in a patient with postencephalitis. Histologically, the process was degenerative in the ganglionic elements and proliferative in the neuroglial elements. These lesions reached their height in the central nuclei of the thalamus (median center of Luys), the striatum and the substantia nigra. In the inferior part of the rolandic zone, cellular changes were observed in the two external layers.

ALPERS, Philadelphia.

GENESIS OF MULTIPLE ENCEPHALOMALACIA AND ANGINA PECTORIS IN FOAM FORMATION. E. LÖFFLER, Frankfurt. Ztschr. f. Path. **47**:239, 1935.

Löffler investigated small but grossly recognizable foci of encephalomalacia located mainly in the basal ganglia and associated with severe sclerosis of the cerebral arteries. These arteries, in most of the cases, were markedly dilated rather than narrowed. He rejects spasm of the arteries as a cause of encephalomalacia without thrombosis because of the rigidity of the vessels. Changes in the blood pressure are, he thinks, not severe enough to cause encephalomalacia. The following explanation of encephalomalacia without demonstrable thrombi is offered: Because of the multiplicity and symmetry of the foci, it seems that embolic occlusions of the vessels must have occurred. The absence of proof of such occlusions is the fault of the methods of examination. For this reason, an experiment was devised during which blood saturated with oxygen was subjected to sudden decrease of pressure. It was found that blood in a glass tube on sudden decrease of pressure becomes foamy. The foam possesses high viscosity and may act in the body like a solid thrombus, producing occlusion of the lumen, at least temporarily. Sudden variations of the pressure in the arteries of arteriosclerotic patients are frequent. The rigidly sclerotic arteries may be compared to the glass tube of the experiment. The most marked decrease of pressure occurs in the small (end) arteries, and the resulting foam thrombi may give rise to the small areas of encephalomalacia. The tortuosity and angular branching of the cerebral arteries likewise would be an important factor in the formation and slow resorption of foam thrombi. Conditions similar to those in the cerebral arteries are observed in the coronary arteries in patients with angina pectoris. Löffler ventures the opinion that the cause of angina pectoris may also be attributed to foam formation.

SAPHIR, Chicago. [ARCH. PATH.]

CARCINOMATOUS CELLS IN THE CEREBROSPINAL FLUID. H. BERTHA, Monatschr. f. Psychiat. u. Neurol. **91**:15 (April) 1935.

Bertha describes two cases of metastatic carcinoma of the brain in which many cancer cells were observed in the cerebrospinal fluid. In one case there was widespread meningeal cancer, and in the other, numerous nodular metastases in the substance of the brain. It is known that meningeal as well as intracerebral metastases are by no means invariably associated with free cancer cells in the cerebrospinal fluid. The cells are observed in the fluid only in an advanced stage of the illness. This indicates that they invade the nervous system long before they appear in the spinal fluid.

Three additional cases are reported which throw light on the question whether metastatic carcinoma reaches the central nervous system through lymphatic channels or by way of the blood stream. In the first case, there was a uterine carcinoma with metastatic involvement of the upper three thoracic vertebrae. Cancer cells filled the epidural space but did not penetrate the dura. They had invaded the nerve roots and spread up the endoneural spaces and perineural sheaths, almost reaching the pia. Nevertheless, there was no evidence of extension of the tumor cells to the meninges. Similarly, in the second case a metastatic growth had extended up the lumbar nerve roots to the cauda equina without involving the meninges. Thus, the fact that cancer cells can reach the central nervous system

by endoneural and perineural lymph channels is no proof that diffuse meningeal carcinoma arises in this way. In the third case there was a bronchial carcinoma with multiple metastatic nodules in the cerebrum. Numerous emboli of cancer cells were observed in the small vessels of the choroid plexus, indicating that the blood stream was the source of the metastatic involvement. Attention is called to the fact that meningeal carcinoma tends to occur at the base of the brain, resembling in its manner of distribution tuberculous meningitis, which is a hematogenous infection. While it is evident that metastases may reach the central nervous system through lymphatic channels as well as through the blood stream, invasion by way of the blood stream is probably responsible for the development of meningeal carcinomatosis.

ROTHSCHILD, Foxborough, Mass.

CONTRIBUTION TO THE PATHOLOGIC PICTURE IN EXPERIMENTAL POLIOMYELITIS. T. ISIZIMA, Psychiat. et neurol. jap. **40**:18 (March) 1936.

Twenty-one monkeys which received intracerebral injections of poliomyelitis virus were studied clinically and histologically. The histologic changes are divided into three stages: (1) the stage of primary parenchymal dissolution with loss of ganglion cells only and absence of mesodermal reactions, (2) the leukocytic stage, (3) the transitional stage from leukocytes to microglia cells and (4) the microglial phase. Lymphocytic infiltration is purely secondary. The microglial stage may persist a long time. The localization of the process is intimately associated with the vulnerability of the tissue. The medulla and spinal cord are most affected. These are followed in order of vulnerability by the cerebellar nuclei, the midbrain, the interbrain and the cerebral cortex. The striatum and cerebellar cortex are but little affected. After intracerebral injection of virus, changes are noted in the medulla and cord in from one to three days and in the cerebral cortex after from six to seven days.

ALPERS, Philadelphia.

## Psychiatry and Psychopathology

THE PSYCHOLOGY OF PRISON LANGUAGE. JAMES HARGAN, J. Abnorm. & Social Psychol. **30**:359 (Oct.-Dec.) 1935.

The language of the criminal shows a highly developed jargon. Its usefulness to him lies chiefly in its emotional rewards. His social rebellion is as effective in his speech as in his more overt behavior; by scorning the conventional vocabulary he doubtless achieves a degree of emotional satisfaction and manages to attach to himself a modicum of that envy and respect which mankind has always accorded to those with ability to speak in unknown tongues. Through cryptic conversations he may acquire a sense of class solidarity and thereby be comfortable in his membership in a group of those who share his speech and, presumably, his problems and destiny.

Despite the fact that generally the parents of the criminal are foreign, he shows no great tendency to borrow from familiar languages, preferring to keep alive a variety of Anglo-Saxon terms. Incongruous as it may seem, he resorts to poetic devices in his urge to express himself vividly. There is observed the constant use of metaphor in which unfamiliar or abstract things are given names of more familiar or concrete objects to which they bear a resemblance; for instance, "bird cage" signifies a prison cell, and "can," a prison. He may try a metonymy (the naming of a thing by one of its attributes or accompaniments, a cause for an effect, etc.), such as speaking of a lawyer as his "mouthpiece" or of a forger as a "scratcher." Sometimes he uses personification or employs hyperbole, as in referring to a revolver as a "cannon." In contrast to this, he may employ understatements or litotes, speaking of a machine gun as an innocent "typewriter" or a year's sentence as "sleeping time." Through this euphemistic understatement, the criminal softens an otherwise too unpleasant reality to something bearable. This escape mechanism is perhaps the essential characteristic of his language. The author lists about 166 prison terms, translating their meanings.

WISE, Howard, R. I.

DREAMS IN WHICH THE DREAMER KNOWS HE IS ASLEEP. A. E. BROWN, J. Abnorm. & Social Psychol. **31**:59 (April-June) 1936.

By the term "lucid dream" is meant the type of dream in which the subject has an appreciation of the fact that he is asleep. Brown, who has himself experienced almost a hundred instances of dreams of this type, claims that frequently he has striven to wake from a dream of this sort but there usually resulted only a false awakening, with the "lucid dream" frequently merging into the usual "nonlucid" type of dream experience. As an example of the lucid type of dream, he relates the following dream experience of F. W. H. Myers (*Proc. Soc. Psych. Research* **4**:241, 1887): "I was, I thought, standing in my study; but I observed that the furniture had not its usual distinctness—that everything was blurred. . . . It struck me that this must be because I was *dreaming*. This was a great delight to me as giving the opportunity for experimentation. I made a strong effort to keep calm, knowing the risk of waking. . . . I therefore wished to see one of the servants; but I was afraid to ring the bell, lest the shock should wake me. . . . As I walked downstairs I looked carefully at the stair carpet, to see whether I could visualize better in dreams than in waking life. I found that this was *not* so; the dream-carpet was not like what I knew it in truth to be. . . . Apparently vaguely generalized from memories of seaside lodgings. . . . The door opened and a servant appeared, quite unlike any of my own. This is all I can say, for the excitement of perceiving that I had created a new personage woke me with a shock." Brown concludes that the cultivation of this variety of dreams seems to be a promising experimental project. WISE, Howard, R. I.

THE CLASSIFICATION OF DEFECTIVE DELINQUENTS. M. J. PAPURT, J. Crim. Law & Criminol. **26**:421, 1935.

Intelligent classification and intelligent human relations have a valuable place in the program of a progressive correctional institution. Doll in 1921 offered a classification of delinquent persons in which a primary grouping was made on the basis of an equal consideration of the factors of intellectual subnormality, mental stability and the degree of recidivism. An etiologic subclassification was included to contain the toxemic, congenitally syphilitic, epileptic, endocrinopathic and environmental types. Branham's classification in 1926 included the following types: (1) the community-conscious, (2) the community-indifferent, (3) the community-antagonistic and (4) the community-irresponsible.

The psychologic classification in use at Napanoch, N. Y., is as follows: idiot, intelligence quotient from 0 to 20; imbecile, from 21 to 46; low grade moron, from 47 to 57; medium grade moron, from 58 to 67; high grade moron, from 68 to 80; borderline type, from 81 to 85; dull normal, from 86 to 92; normal, from 93 to 107; superior, from 108 to 113; very superior, from 114 to 130, and gifted or genius, 131 and higher. The psychiatric classification is based on: (1) sexual predominance; (2) defective predominance, and (3) delinquent predominance. The administrative classification, based on institutional behavior, includes: (1) the adjustable; (2) the chronic offender, and (3) the segregatable, including the sex offender, the hopeless major offender and the occasionally disturbed patient. This classification is offered as the result of a study of 1,500 inmates in the Institution for Male Defective Delinquents at Napanoch, N. Y. SELLING, Detroit.

THE CLASSIFICATION OF FELONS IN A MID-WESTERN STATE PENITENTIARY. EDGAR W. VOELKER, J. Crim. Law & Criminol. **26**:883 (March) 1936.

The idea of punishment has motivated the penal methods of both ancient and modern societies. Because it has proved ineffective in reforming criminals, a new philosophy has developed which regards the offender as a maladjusted person and seeks to diagnose and treat his social illness much as a physician diagnoses and treats a physical illness. Such an approach requires a classification of offenders which is based on individual study. This article describes and criticizes the attempt, in 1933, of a midwestern state penitentiary to execute such an approach

in practice. Diagnostic depots were established, in charge of three experts; a psychiatrist, who examined the offender for mental disease; a psychologist, who determined his mental age, and a sociologist, who recorded his social history and various group rôles. The object in obtaining these facts was to use them as a basis for segregating offenders by personality type. Such a segregation was thwarted by the persistence of older methods of classification, e. g., (1) the warden retained some men when they were financially useful, regardless of their personality type; (2) the artificial distinction between "first offenders" and "habitual criminals" was used, and (3) unrestricted contacts were permitted between normal, psychopathic and mentally deficient inmates. Moreover, inadequacies of plant equipment and social organization defeated the purposes of the new plan, e. g., (1) only one prison unit gave vocational training which was useful after release; (2) educational and library facilities were markedly inadequate; (3) recreation was limited and lacked direction and coordination; (4) administrative personnel was politically appointed and had no professional preparation, and (5) discipline was standardized and formal. "These difficulties were largely due to the conflict between the scientific attitude and procedure, and the attitude of punishment in terms of which the existing prison procedure is organized."

SELLING, Detroit.

A STUDY OF RUNAWAYS AT A STATE CORRECTIONAL SCHOOL FOR BOYS. CORNELIA R. KEOGH, J. Juvenile Research **19**:45 (April) 1935.

The object in this study was to determine what factors might differentiate the runaway boy from the general group of delinquents. The records of 200 runaway boys were compared with those of 400 boys admitted consecutively. The most significant differences between the groups were that there was a greater percentage of broken homes for the runaway group and that a history of previous running away from home and previous truancy from school was more common in the group of runaway boys. The past institutional adjustment was less satisfactory in this group than in the group of children who did not run away. Boys run away most frequently during the early months of their stay at the institution. Fifty-one per cent of the group leave only once; 25 per cent run away twice, and 10 per cent, three times. The percentage of truants in the general population is 17.29. The months of October, December and August were the favorite months for running away, while February, July and March were months of the lowest number of escapes. Seasonal variations were slight. There were minor differences between the two groups, when they were compared from the standpoint of the level of intelligence, age, race, parental occupation and proximity of the child's home to the institution.

FERGUSON, Niagara Falls, N. Y.

THE UTILIZATION OF PLAY IN THE CONSTRUCTION OF HEALTHY MENTAL ATTITUDES. JOHN EISELE DAVIS, Ment. Hyg. **20**:49 (Jan.) 1936.

Normal children often have unhappy play experiences, becoming resentful and discouraged in losing or unduly elated in winning; these are irritated by disappointing toys and restrictive rules. This fact may be compared to the disastrous effects of false ideals and ideas of play in the formative period of the lives of the mentally ill. Ideally, emphasis must be placed on striving together toward a reward more satisfying than the egotistic compensation of the lone winner, to the exclusion of other players. An experimental survey, in which discussion of the personality situations involved played a large rôle, revealed that boys were genuinely interested in talking about something that they had actually done; discussion of the game convinced them of the value of qualities such as humility, good sportsmanship, honesty and friendliness, as well as of the qualities of physical strength and skill. Scrutiny of individual play enabled each one to feel that he had accomplished something worth while.

Davis believes that, in conducting a program of physical education for the mentally ill, more healthful mental attitudes can be fostered and that more wholesome satisfactions can replace the selfish aggrandizement of a lone person by

emphasizing through these informal discussions the richly significant relations of the physical acts to wider social practices. Practicable applications of the modifiable play experience to the higher moral and social values and appreciations may possibly offer important educational opportunities in the future.

DAVIDSON, Newark, N. J.

SYMPTOMATIC PSYCHOSES WITH BROMIDE INTOXICATION. PAUL W. PREU, JOHN ROMANO and WARREN T. BROWN, New England J. Med. **214**:56 (Jan. 9) 1936.

There are certain dangers in using bromides as sedatives, and the frequency of bromide intoxication in southern New England forms the basis of this paper. Since the principal action of bromide is its depressing effect on the central nervous system, it becomes a valuable drug in the treatment of epilepsy and other mental disorders, such as the tensional states in which anxiety and insomnia are prominent complaints. Intoxication by continued medication is due to displacement of the chlorides in the blood by the bromide ion. Chloride is excreted in the urine in greater proportions than bromide. The two salient points in the symptomatology of this syndrome are delirium and the apparent independence of cutaneous and psychiatric symptoms. There may be exaggeration of the pharmacologic effect, and even psychosis. A definite diagnosis of bromide intoxication can be made only by its identification in the blood and urine, which is done by a modification of the method of Walter and Hauptman. A bromide level in the blood of 250 mg. per hundred cubic centimeters is found in bromide psychoses, and severe intoxication occurs when 30 per cent of the blood chlorides is displaced. The delirium is due to the presence of bromide and not to the absence of chloride. The authors found that 2.5 per cent of patients admitted to the New Haven Hospital showed indications of bromidism; they report nine cases in detail.

They conclude that bromides are clearly indicated in the treatment of certain patients with common organic diseases and that a fairly large amount can be given with safety if the chloride-bromide balance is maintained. This group of drugs is contraindicated in excited states; paralydehyde is preferable in such cases. Bromide should be used with caution in arteriosclerosis and nephritis, and should never be used in states of dehydration or malnutrition. The presence of a cutaneous eruption during bromide medication is not a clear indication of intoxication. An eruption of the skin occurred in only six of the nine cases and was in no instance severe enough to require treatment. Bromide intoxication occurs without the presence of a cutaneous rash.

KRINSKY, Boston.

WORDS AND MASSES—A PICTORIAL CONTRIBUTION TO THE PSYCHOLOGY OF STAMMERING. W. J. SPRING, Psychoanalyt. Quart. **4**:244, 1935.

Spring describes the finger paint production of a boy of 10 who had stammered since the age of 5 years. Both the content of these paintings and the boy's behavior while he made them are important. He came to a painting class with a reputation of being irritable and extremely careless. In the new class he at first refused to touch the paint, gave the teacher a false name and made fun of the productions of other pupils. After a while, he secretively began to paint, using more paint than was necessary and being contemptuous of his results. He was openly envious of the skill of other children, continued to criticize their work and often splashed them with water or accidentally bumped their work. After two months of this behavior, during which he worked exclusively with blacks and obviously made no recognizable pictures, he gradually evinced more interest in the teacher and began to paint. His first described painting was in a dark reddish brown and depicted words falling from the mouths of two women in the next room. For the next two or three weeks, he continued to paint words in black or brown. All words had specific shapes; e. g., "she" was two globes connected by a double line.

At this point he became more confidential with the teacher and told her that the other children did not like him because he smelled. The teacher discussed

methods of personal cleanliness with him, and he was much surprised when he learned that she too had to defecate. Shortly after this, he told her that he stuttered because of the shapes of words. Easy words came out easily because they were shaped like sausages and were liquid. Other words stuck and caused him to stammer because they had corners or were square. "Hour" was big and round in the middle and had four little knobs on each end. "Fear" was a line with two knobs on each end. "Home" had many jagged edges. The name of a teacher whom he disliked had many prickles on it, while the name of his painting teacher, whom he liked, was liquid and did not cause him to stammer. As soon as this had been discussed, he ceased painting shapes of words and began to use bright colors, always painting a story represented by streamers emerging from a treelike trunk. He became more friendly with his teacher, and his stammering improved while with her, although he continued to stammer badly with persons whom he disliked. Shortly after this, he was withdrawn from the school, and observations of him ceased.

Spring points out that this case gives an unusually vivid illustration of several important dynamic factors in stammering. These are: 1. The unconscious identification of words with feces. 2. The unconscious identification of words with an introjected object. The patient stammered because of the prickles on the name of the teacher whom he disliked; i. e., the conflict between the subject and the object (teacher) was expressed by a conflict between the ego and its speech apparatus and products. 3. The identification of the body with a penis from which emerge exhibitionistic, urethral and anal products.

According to the painting teacher, five or six stammerers have shown improvement. Perhaps the invitation to smear justifiably in painting offered the children a situation well suited to overcome the sense of guilt connected with anal wishes. The teacher, being really interested in the painting, could put a high value on the products of this smearing activity, making them the source of object-directed gratification. By this the fecal mass would become raised to the level of a gift, making possible a partial use of the anal conflict, at least in relation to the teacher.

PEARSON, Philadelphia.

THE SOCIOLOGICAL SIGNIFICANCE OF COMMUNISM CONSIDERED IN THE LIGHT OF PSYCHO-ANALYSIS. W. R. D. FAIRBAIRN, Brit. J. M. Psychol. **15**:218, 1935.

This article is an application of psychoanalytic thought in the field of sociologic study and is concerned with an analysis of the noneconomic motives which lie behind the communistic movement. The discussion is framed around two of Freud's concepts, the libido and the Oedipus situation.

Libido binds individuals into social groups, and the "cohesion of a group depends upon the extent to which the libido is bound within the group." The family constitutes the original social group, and its cohesion depends partly on the libido being bound within the group but also on exclusion of aggression. The Oedipus situation provides the portal of entry for rivalry and aggression and hence is the main threat of disruption of the group. To guard against this disruption, the primitive patriarchal cultures made incest and patricide the two great crimes; the stringent taboos which developed to prevent these crimes operate as strongly in civilized as in primitive man. Therefore "taboos upon incest and patricide are undoubtedly the cultural mainstay of the family and consequently the foundation upon which all higher forms of social organization rest."

In the evolutionary scale, the clan is the next social group and is formed partly to replace the family group, but since the clan is also organized around family lines, with a chief or father, it is still faced with the danger of binding the libido into too narrow limits; there is also the danger of the libido finding attachment outside the clan, which would lead to a less cohesive group. Hence, the clan did not constitute a stable social institution and was replaced by the tribe as a union of clans. In the tribe, exogamy is practiced by allowing marriage between members of component clans, obviating thereby the necessity of marriage outside the tribal groups but, at the same time, avoiding "technical incest." Thus, the tribe

became a more stable form of organization than the family or the clan. As the clans comprising the tribal organization weakened, the nation evolved as the next social group, a form of organization that has now supplanted the tribe throughout the civilized world.

Through these various types of social organization, the family has persisted, but there has been continual conflict between the family and the state, with the state gradually encroaching on the province of the family in taking over many of its functions. In spite of this conflict, the family has persisted as a sociologic and biologic institution.

Communism represents a social system even more comprehensive than the nation, and a further step toward weaning the individual away from basic loyalty to the family and replacing the communistic state as the one object of every one's loyalty. The unconscious aims of communism involve, therefore, the destruction not only of the nation but of the family. The communistic ideal admits no loyalty except that to a world state. Since the Oedipus situation is inherent in the family system, the only hope of eradicating the Oedipus conflict in individual minds lies in the destruction of the family as a social group. If communism accomplishes this goal of eradicating the family, it will, at the same time, accomplish the removal of the taboos on incest and patricide which keep the Oedipus conflict in a state of repression in the unconscious. The unconscious motive, therefore, of the whole communistic movement is a further attempt on the part of man to rid himself of the shackles imposed by the Oedipus situation.

ALLEN, Philadelphia.

BRAIN SIZE AND MENTALITY. R. J. A. BERRY, Brit. M. J. **2**:62 (July 11) 1936.

By means of measurements of the brain a product can be calculated as an index of cerebral size. The material studied consisted of thirty-nine normal brains of persons of both sexes and various ages and seventy brains of defective persons, sixteen of whom were mongolian idiots. The left cerebral hemisphere was removed and prepared for subsequent histologic examination; the right half of the hardened brain was placed in a dioptrograph, and a life-size tracing was made of the external, or lateral, surface. On these tracings, measurements, angles and planimeter readings of size could be made with a high degree of accuracy. Cerebral breadth was measured by this diagraph. A simple and reliable index of brain size may be obtained by multiplying the figures for length, breadth and height and taking the first three digits of the calculation as the index product of brain size. The index product for twenty-eight normal brains was 247. It then becomes possible to establish direct comparisons between the size of the brain and that of the head during life. It has already been shown that growth of the brain practically ceases in normal children between the eighth and the eleventh year of life, whereas the head continues to show a slight increase in size for several years after. During the period of brain growth there is therefore a distinct and measurable relationship between the size of the head and that of the brain. It is frequently of clinical importance to know whether or not a child's brain is keeping pace with his chronological years, and this fact may be ascertained within the limits of present knowledge from measurements of the head.

These investigations suggest that mental deficiency, in the great majority of instances, is the result and consequence of a brain too small for its proper functions and that this cerebral deficiency affects the whole central nervous system. It may be said that an underdeveloped central nervous system does not function properly and that this imperfect functioning resembles the disturbances produced in a previously normal nervous system which has been the subject of disease processes. In addition to the mental state, the pronounced epileptic and diplegic phenomena presented by some defective persons may be due to, or aggravated by, abnormal proportions of the precentral and postcentral cortex. Since most, if not all, of these features of the defective brain are embryologic in character and nature, they are of prenatal origin and are not as commonly due to "birth injuries" as is generally supposed. If, therefore, mental deficiency is defined as a departure

from the standards of normal growth, the genetic factors concerned would appear to be those associated with growth in general and not mentality in particular.

That the basal ganglia share with the cortex diminution in size is probable, though the point has not yet been fully examined. If this is true, it is not unlikely that some pathologic states usually regarded as symptomatic of striatal disease may really indicate a much broader and more widespread involvement of the nervous system as a whole, especially of the neopallial cortex.

The microscopic features are under investigation, but observations are as yet incomplete. Instances have been observed in which the defective supragranular cortex is thinner than normal. Micrometric measurement of the cortical laminae shows, on the average, no significant difference in the mean between the defective and the normal brains. In this respect these observations differ from some earlier ones. On the other hand, these investigations strongly support the view that a disorderly arrangement of the cells of the cortex is a feature of the defective brain. In fact, it is by these qualitative changes that the defective cortex may most easily be distinguished from the normal. The defective cortex shows many variations from the normal in its cellular construction, more especially in the supragranular layers. Thus, in some instances there are small supragranular neurons, with reduction in the amount of stainable cytoplasm in the third lamina. In others there is a great increase in the number of pyramidal cells per unit of the count.

The textbook picture of the cortex is commonly encountered in normal brains used as controls but is not seen in the range of defective brains, and the defective cortex tends to show abnormal cyto-architectonic features more frequently than the normal. While the purely cytologic approach to the detection of cortical differences between a "poor" normal brain and a "good" defective brain can never be easy, and may indeed escape one altogether, it is nevertheless permissible to suggest, as does this investigation, that in the majority of defective brains there has been some inhibition or distortion of the factors making for normal neuronic growth and organization.

BECK, Buffalo.

PERSONALITY CHARACTERISTICS OF HAPPILY MARRIED, UNHAPPILY MARRIED AND DIVORCED PERSONS. WINIFRED BENT JOHNSON and LEWIS M. TERMAN, Character & Personality **3**:290 (June) 1935.

Responses to the Bernreuter personality inventory and the Strong vocational interest test of 100 happily married, 100 unhappily married and 100 divorced couples are statistically analyzed. Roughly, a third of the items yielded from one to several differences large enough to approach statistical significance. Johnson and Terman outline a composite picture of each of the groups. Traits of the happily married couples include emotional stability, social adaptability, uplift interests and a tendency to conservatism, the men showing more tolerance and sympathy than the women. Unhappily married persons gave most evidence of neurotic and introvertive tendencies, intolerant attitudes and volitional inadequacy. The unhappily married woman is closer to the happily married than to the divorced woman, and the unhappily married man is closer to the divorced than to the happily married man. The group of divorced women are characterized by self-reliance, independence, tolerance, initiative and conative intensity. The divorced of both sexes have more intellectual interests than either of the married groups.

MATHER, New Haven, Conn.

THE SIGNIFICANCE OF THE FRONTAL LOBES FOR MENTAL PERFORMANCES. K. GOLDSTEIN, J. Neurol. & Psychopath. **17**:27 (July) 1936.

In the proper evaluation of the significance of the frontal lobe for psychic performance, the following considerations must be borne in mind: 1. The site, extent and nature of lesions of the frontal lobe. These must be localized in the prefrontal region of both hemispheres, or at least of the left, depending on cerebral domi-

nance, and must be extensive enough, varying with the nature of the lesion, to produce definite mental disturbances. 2. The methods of examination must be adequate to disclose the psychic alterations. In analyzing the symptomatology of such lesions with the proper methods, a number of faulty reactions are disclosed which indicate a basically changed behavioral attitude rather than a fundamental change in any single performance or field. Thus, disturbances occur in apprehension of spatial and temporal relations, in situations requiring selection between several possibilities, in finding out the essence of a situation and in the approach to a situation which is presented only in imagination or which demands readjustment. Such situations give rise in the patient to partial reactions or perseveration, with resulting confusion, excitement or akinesis. The frequently observed changes of affect in these conditions, such as emotional dulling, groundless excitement or witticisms, are to be regarded not as emotional defects but as appropriate reactions, when one considers that the patient grasps only a part of the situation. In the same way, alterations of memory and attention are not actual defects but vary with the situation according to its concrete or abstract nature, the patients succeeding in the first type and failing in the second. Memory appears impaired because the abstract situation normally plays an important rôle in the acquisition and reproduction of facts.

According to Goldstein, these disturbances can be understood only when one considers that there are two kinds of human attitude toward the world: (1) a concrete attitude in which one is directed toward given objects and is directed in thinking and acting by them and (2) an abstract attitude in which one is moved at first to think about the objects and to give an account of them to oneself. To each belongs a particular type of behavior; some tasks can be performed only by the one and others only by the other. In cases of lesion of the frontal lobe there are disturbances in the different fields of psychic performance, but no field is disturbed throughout its extent or is the basic cause. The fundamental change consists in a disturbance of the abstract attitude, which finds expression in certain performances in all fields. Physiologically expressed, it represents disintegration of a higher, more complicated process, determined by the whole organism, to a less complicated, lower one, determined by the stimuli of the outer world. In the symptomatology of lesions of the frontal lobe other functions of the frontal lobe must be considered. These are maintenance of body equilibrium and control of direction and certain motor activities connected internally with the psyche, such as speaking and writing. In diffuse involvement of the entire cortex the symptoms are to be regarded as manifestations of damage to the frontal lobes, since the highest function is always the first to be disturbed. This explains the similarity between diffuse involvement and lesion of the frontal lobe; considerations of the total psychic and somatic picture will alone differentiate between them.

N. MALAMUD, Ann Arbor, Mich.

INFLUENCE OF CHRONIC EPIDEMIC ENCEPHALITIS ON SCHIZOPHRENIA. J. DRETLER, Encéphale **30**:655, 1935.

Dretler reports three cases of schizophrenia in which epidemic encephalitis developed and was followed by chronic parkinsonism. In all three instances the schizophrenic manifestations, including auditory hallucinations, disappeared. The encephalitis and its sequelae followed their usual course. In one case encephalitis ushered in transient visual hallucinations; in another case there were obsessions accompanying oculogyric crises. These manifestations are believed to be correlated with encephalitis and not with schizophrenia. In one case catatonia disappeared while parkinsonism developed. Dretler considers this an argument against the hypothesis that schizophrenic motor disturbances are of subcortical origin. To explain the disappearance of schizophrenic manifestations, he suggests that chronic encephalitis may interfere merely with the exteriorization of the schizophrenic process. The latter may persist in a latent form.

LIBER, New York.

SENILE EROTISM IN WOMEN. EUGENE GELMA, Encéphale **30**:737, 1935.

Senile erotism usually appears in women aged from 65 to 70 who have, as a rule, been very reserved. There may be obsessive and exhibitionistic manifestations of erotism. Hormonal disturbances do not offer a satisfactory explanation. Gelma believes that impairment of inhibitory functions, first affected by the cerebral dissolution of senility, as well as by that of various dementias, is the immediate cause of senile erotism. The lifelong repression of the sexual urge, more intense in women than in men, predisposes women to sudden, exuberant sexuality when the inhibitions are removed. Treatment consists of sedation and psychotherapy. The latter comprises chiefly an appeal to sentiments of modesty, dignity and honor which the patients may retain. An apparent disappearance of erotism may be only a remission. In some cases the manifestations are recurrent and may be more or less regularly cyclic.

LIBER, New York.

JOY WHICH CURES. C. PASCAL and J. ROYER, Hyg. ment. **30**:157 (Sept.-Oct.) 1935.

This is an account of an unusually interesting case in which a strong emotion seemed to influence markedly a condition of very chronic nature. A woman who had had serious domestic discord lost her husband in the World War. This was followed by an acute mental disturbance. Some years later there had developed well formulated auditory hallucinations, delusions of persecution and a series of symptoms, including mannerisms, mutism, incoherence of language and other more serious symptomatic manifestations. Although visited frequently by her son, she was under the conviction that he was being held a prisoner. This state continued for several years. Finally, the son brought his wife to visit the patient. Almost in an instant the patient's entire reaction changed. She was overcome with joy at the discovery that her son was happy and accepted with deep satisfaction the presence of the new daughter-in-law. From this time the clinical picture changed. It is true that the hallucinations continued, but they lost their personal and disturbing character. In every other way she returned to a normal reaction pattern. Pascal and Royer think that there has been inadequate concern among psychiatrists with the therapeutic effects of hypersthenic emotions.

ANDERSON, Los Angeles.

POSSIBILITIES OF SURGICAL TREATMENT IN TREATMENT FOR CERTAIN PSYCHOSES. EGAS MONIZ, Lisboa med. **13**:141, 1936. THE FIRST TRIAL OF PSYCHOSURGERY: TECHNIC AND RESULTS. EGAS MONIZ and ALMEIDA LIMA, ibid. **13**:152, 1936.

The profound changes in character that occur after injury of or operation on the frontal lobe and various diseases in this region led Egas Moniz to the concept that destruction of the subcortical white matter in the prefrontal lobe might be followed by improvement in the mental state of some patients with psychoses. By means of an instrument called a leukotome, he destroyed the fibers in the white matter underlying the tip of the frontal lobe on both sides. This was carried out on twenty patients, of whom seven recovered, seven improved and six showed no change in the condition. The best results were obtained in cases of anxiety neuroses and involutional depression. Egas Moniz believes that psychiatry has entered into the organic or neurologic phase and points out that neurologic orientation has brought about a remarkable progress in psychopathology.

FREEMAN, Washington, D. C.

SYPHILITIC DISEASES OF THE NERVOUS SYSTEM IN BURIAT MONGOLIANS. B. BERINGER, Arch. f. Psychiat. **103**:357 (June) 1935.

Beringer was a member of a joint Russo-German expedition into a Siberian district, with the purpose of studying the pathologic and clinical features of syphilitic diseases. He reports his observations in relationship to the nervous

system. One of the points of particular interest was the attempt to investigate the tenability of the theory advanced by Wilmanns, according to which there is a certain relationship between the occurrence of dementia paralytica and tabes and the intensive treatment of primary syphilis.

Beringer comes to the following conclusions: In this rather primitive social group, where endemic syphilis has existed for the last one hundred and fifty to one hundred and eighty years and where treatment has been carried on for only about eight or ten years, there were essentially two types of syphilis: one with marked lesions of the skin, mucous membranes, bones and central nervous system and another, the so-called adermotropic type, in which the syphilitic infection could be definitely demonstrated only serologically, with few clinical signs. These two groups are each represented by about 50 per cent of the patients examined.

In refutation of a great deal that has been written on the relationship between the occurrence of tabes or dementia paralytica and the more advanced civilization and culture of a particular locality, Beringer found a fairly large number of cases of both these diseases in the district in which he worked. Thirty-three such cases were studied, in only 5 of which the disease had been treated before the manifestations of changes in the central nervous system.

The author did not find the usually reported antagonism between tertiary syphilis and metasyphilis. Of 265 cases of so-called latent syphilis 3 were of dementia paralytica, 9 of the tabetic form of dementia paralytica and 11 of tabes. Of 172 cases of tertiary syphilis 2 were of dementia paralytica and 8 of tabes. Proportionately, therefore, one finds little difference between the two types.

W. MALAMUD, Iowa City.

## Meninges and Blood Vessels

EPIDEMIC LYMPHOCYTIC MENINGO-ENCEPHALITIS: A REPORT OF THIRTY-SEVEN CASES OCCURRING IN PHILADELPHIA. ERNEST L. NOONE, KARL HABEL and HELEN E. RIGGS, Am. J. Dis. Child. **52**:870 (Oct.) 1936.

The authors present clinical and laboratory findings in thirty-seven cases of epidemic meningo-encephalitis in children. The disease was communicable. The period of incubation averaged from five to nine days. The onset was either abrupt or insidious. The duration was usually from three to six days. Fever averaged from 101 to 103 F. and lasted from two to seven days. Headache was the most constant complaint and was almost always promptly relieved by the withdrawal of spinal fluid. Vomiting occurred in thirty-two patients, many of whom complained of abdominal pain or tenderness. Twenty-seven children had nuchal rigidity. Fourteen showed a positive Kernig sign and one a positive Babinski sign. There were no constant alterations in tendon reflexes. Four patients had chills and seven photophobia. There was usually no noteworthy inflammation of the nose or throat. Examination of the spinal fluid showed normal pressure readings, pleocytosis of variable degree, with lymphocytes greatly predominating, and a normal content of sugar and chloride. Pleocytosis usually persisted for several days. Blood counts and urinalyses yielded no especially abnormal results. Experimental animals given injections of spinal fluid, blood serum and nasal washings from patients in the acute phase of the disease and of suspensions made from the brain and spinal cord of a patient who died of the disease showed no evidence either clinically or pathologically of anterior poliomyelitis, acute encephalitis or acute choriomeningitis. Convalescent serum from these patients did not neutralize known viruses of anterior poliomyelitis, acute choriomeningitis or the St. Louis type of acute encephalitis (encephalitis B).

Pathologic study of the brain and spinal cord of a patient who died showed intense edema and diffuse cellular degeneration, especially of the second and third layers of the cortex, the Purkinje cells, the vegetative nuclei of the medulla and tuber cinereum and the anterior horn cells. There was sparse perivascular cuffing and practically no glial reaction.

WAGGONER, Ann Arbor, Mich.

MENINGITIS DUE TO BRUCELLA IN A CHILD. MARY A. POSTON and ROBERT H. THOMASON, Am. J. Dis. Child. **52**:904 (Oct.) 1936.

Poston and Thomason report the case of a girl with low grade, subacute meningitis due to Brucella abortus who recovered completely after repeated spinal punctures and intraspinal injections of human immune serum. It is possible that conditions diagnosed as tuberculous meningitis in which no organisms were seen on direct smear and some in which "influenza-like" bacilli were seen but not cultured may have been meningitis due to Brucella.

WAGGONER, Ann Arbor, Mich.

OSTEOMYELITIS OF THE FRONTAL BONE: NOTES ON THREE CASES. H. P. MOSHER, J. A. M. A. **107**:942 (Sept. 19) 1936.

Mosher reports three cases, in two of which there was a fatal outcome. He says that he is convinced even more strongly than in his report of three years ago that edema of the skin of the forehead is a rough guide to the extent of infection of the the bone and periosteum. If there is actual bone necrosis, the bone is infected without necrosis for from an inch (2.54 cm.) to an inch and a half (3.81 cm.) beyond the necrotic area. Bone necrosis does not occur until from seven to ten days after pitting edema appears, and the roentgenogram is not positive until necrosis appears. Examination of the specimen of bone removed in two of the cases reported showed that the infection spreads along the inner surface of the bone, as well as by the diploic veins. When the infection spreads by way of a diploic vein, it may localize at a point far from the original source of infection. When it does so localize, the pus tends to work both inward and outward, giving either a subperiosteal abscess or an extradural abscess or both, with destruction of the bone between the two. When a condition has lasted two or three weeks, the operator should expect to find one or both of these conditions. Histologic examination of the author's specimens shows, in addition, that the infection may spread by way of an inner layer of new bone which is formed between the skull and the dura. The small veins which run in the new bone are often infected, and there are numerous hemorrhagic clots which also are infected. Further, the infection spreads by way of the fibrous tissue which covers the new bone and binds the inner surface of the skull to the dura. The operator who is performing his first operation in a case of osteomyelitis of the skull should expect an extradural abscess as a matter of course. In fact, he should expect more than this; he should be on the lookout for a subdural or a brain abscess. The brain abscess, if present, is usually seen later or comes later as a complication, but it is always round the corner and should be watched for, even at the first operation. The more Mosher sees of osteomyelitis of the frontal bone, the more he believes that the whole face of the frontal bone should be removed as a routine, from the hair line to the eyebrow. Preferably, it should be removed in one piece. However, if the patient is in poor condition and there is an area of necrosis, it is justifiable to work from the necrotic area outward, removing the bone for from an inch to an inch and a half in all directions from the necrotic area. He believes further that both frontal sinuses should be opened and the anterior and posterior walls of each sinus removed. He believes strongly that the lateral limit of the bone flap on each side should be at least the outer angle of each frontal sinus or, better, the outer angular process of the frontal bone on each side. The objection to this extensive removal is the deformity. It has been proved that fully 90 per cent of this can be corrected by modern plastic surgery. Therefore the surgeon should not allow his hand to be halted by the question of deformity. If he does, he will lose most of his patients with osteomyelitis of the skull.

EDITOR'S ABSTRACT.

ACUTE LYMPHOCYTIC MENINGITIS. HENRY R. VIETS and SHIELDS WARREN, J. A. M. A. **108**:357 (Jan. 30) 1937.

Viets and Warren report their further experiences with acute lymphocytic meningitis from the clinical point of view, especially with regard to variations in its severity, and the results of pathologic examination of the tissues in one case. The three cases reported illustrate three types of the disease: fatal, prolonged and severe and transient. In these cases, as in those previously reported, the clinical syndrome varies only in degree and not in character. No new signs or symptoms have been discovered. In case 2, however, the lymphocytes appeared in the cerebrospinal fluid in larger numbers than had previously been suspected, reaching a level of nearly 4,000 per cubic millimeter at the height of the disease. The protein content, too, was higher than had previously been recorded—498 mg. per hundred cubic centimeters before any blood had entered the cerebrospinal fluid. These high readings do not appear to justify a change of diagnosis, although the persistence of such a high cell count may well postpone the correct diagnosis, as it did in this case. The sugar level, which fell to 40 mg. per hundred cubic centimeters, has also not been observed before. This suggested tuberculous meningitis, until a turn upward on the following day was distinctly in favor of a diagnosis of benign meningitis. Case 3 is described merely by way of contrast, to show how mild the disease may be and how transient the symptoms. In case 1, so far as is known, the first necropsy was performed in this disease. Clinically and serologically the case does not appear to be different from many others that have been reported. The cell count was not higher than is commonly observed; the cerebrospinal fluid pressure was much increased, but this has been a not uncommon finding, and the protein and sugar contents and the colloidal gold curve were not abnormal for the disease. The chloride level, however, on the one occasion on which it was determined was lower than the authors have usually seen in this disease. The clinical course, moreover, was not unusual, except for the terminal convulsions. The pathologic changes were surprising. Instead of being confined to the meninges, the lesions were widespread throughout the central nervous system, and encephalitis, as well as meningitis, was marked. With such evident encephalitis it might well be questioned whether one should classify the condition in this case as acute lymphocytic meningitis. Clinically the disease conformed to the accepted diagnosis, and the appearances in the cerebrospinal fluid were consistent with what little is known about the disease. Further studies in the pathology of this syndrome are needed. The reaction of the nerve tissue was severe, although the pathologic appearance did not preclude recovery. EDITOR'S ABSTRACT.

ANEURYSMAL DILATATION OF THE OPHTHALMIC ARTERY, CAUSING SUPERIOR PSEUDOHEMIANOPIC CONTRACTION OF THE VISUAL FIELD. T. DE MARTEL, J. FRANÇOIS and J. GUILLAUME, Rev. d'oto-neuro-opht. **14**:633 (Nov.) 1936.

The case reported was that of a man aged 38 who for the preceding three months had noticed disorder of vision in the right eye. Examination revealed superior hemianopic narrowing of the visual field of the right eye, with abolition of the photomotor reflex in the blind part of the retina, slight hypertension of the cerebrospinal fluid with albuminocytologic dissociation, hyperglycorrhachia and papillary congestion. Eleven weeks after his admission to the hospital, the narrowing of the visual field had progressed; vision was diminished to one-half, and the tension of the retinal artery was increasing. A lesion of the optic nerve, lying between the sella turcica and the orbital part of the optic canal, was postulated. Exploratory operation revealed that the right optic nerve was compressed by dilatation of the ophthalmic artery in the vicinity of the optic foramen. Pressure was relieved by enlarging the foramen upward. Recovery was prompt. One month after operation the photomotor reflex was normal; papillary congestion had disappeared; the tension in the retinal artery was normal; visual acuity had diminished to one-third, and the right visual field had increased upward by 5 degrees. Objects situated in the superior visual field were dwarfed.

Aneurysm of the intracranial portion of the ophthalmic artery is rare. The two principal causes of nontraumatic aneurysm of an intracranial artery are congenital degeneration of the middle tunic of the artery and septic embolus from infectious endocarditis. In the case reported, infectious endocarditis could be excluded. Perhaps the cause of the condition was congenital degeneration of the middle tunic of the artery, but, on account of the slight lymphocytosis in the cerebrospinal fluid and the hyperglycorrhachia, syphilis had to be borne in mind, although no clinical or cytologic symptom of it was elicited.

DENNIS, San Diego, Calif.

PATHOGENESIS OF TUBERCULOUS MENINGITIS. CHRISTIANNE RADMANN, Virchows Arch. f. path. Anat. **295**:563, 1935.

Ten brains with tuberculous leptomeningitis were examined, with the aim of determining the correctness of Rich's view that in the majority of instances tuberculous meningitis is the result not of hematogenous infection of the meninges but of the spread of an older cerebral or meningeal focus. The observations in three of the ten brains are held to confirm Rich's contention. In each of these there was an older process with terminal miliary tuberculosis; i. e., there were cerebral tubercles older than the terminal miliary lesions. Four brains showed progressive primary tuberculosis with overwhelming terminal involvement. Radmann believes that meningitis of this type can be distinguished histologically from that secondary to an older lesion of the brain or meninges. The conditions in the remaining three brains are placed in an intermediate group. In one of these there was a solitary tubercle of the brain, but histologically the meningeal process was held to be like that of the second group. In the other two specimens a primary complex could not be observed.

SCHULTZ. [ARCH. PATH.]

## Diseases of the Brain

MYOCLONIC EPILEPSY OF UNVERRICHT: REPORT OF TWO FAMILIAL CASES. EUGENE ZISKIND, Bull. Los Angeles Neurol. Soc. **1**:59 (June) 1936.

Ziskind describes the cases of two sisters, the elder of whom at the age of 11 years began to have irregular movements resembling electric shocks in various parts of the body, particularly the abdominal muscles. These were worse in the morning, were increased by observation or irritation and eventually became so severe as to throw the patient to the ground and cause fractures. When first seen in 1930 (at the age of 13), she was considered to have a form of chorea and was treated unsuccessfully with phenobarbital and sodium cacodylate. Two months after this examination she began to have generalized convulsions, after which the mother remembered former attacks of momentary loss of consciousness and nocturnal spasms of the extremities with unconsciousness. Examination in 1933 (at the age of 16) revealed slight obesity, some mental retardation, irregular clonic spasms of practically all the muscles of the body, including the tongue and abdominal muscles, and a myoclonic reduplication of the Babinski response on the right. Whenever the abdominal muscles were involved, the movement was symmetrical on the two sides. The Chvostek sign was positive and the Trousseau sign negative. The myoclonic jerks sometimes interrupted speech and respiration. All laboratory tests, including examination of the spinal fluid, gave normal results, but three estimations of the cholesterol content of the blood gave results of 173, 226 and 192 mg., respectively. Encephalography and electrical tests of the muscles revealed no definite abnormalities. Both the myoclonus and the convulsions became steadily more severe, and the patient began to exhibit slow, tremulous speech. No improvement was noted on treatment with calcium and preparations of pituitary, but brief improvement occurred when a ketogenic diet was given.

The patient's sister, aged 7 years, had begun to exhibit involuntary jerkings of the arms and a tendency to drop objects. Examination revealed frequent petit

mal attacks, during which there were quick movements first in one arm and then in the other. There were also generalized roughening of the skin and enlargement of the liver, spleen and inguinal lymph glands. The laboratory findings were normal, except for eosinophilia of 13 per cent.

MACKAY, Chicago.

HYPEROSTOSIS FRONTALIS INTERNA. SHERWOOD MOORE, Surg., Gynec. & Obst. **61**:345, 1935.

The term was first employed by Moore and by Morel almost simultaneously to designate a peculiar condition occasionally found in the frontal bone, associated with which were mental disturbances and obesity. The lesion is by no means the medical curiosity that statistics appear to make it, for to the sixty-five cases recorded in the literature seventy-two other examples have been added. Regionally, the cases can be classified into those in which the hyperostosis is confined to the squamous portion of the frontal bone, those in which it is confined to the orbital plate and those in which it occurs in both these portions. The other bones of the cranium appear not to be involved. The thickening of the frontal bone does not extend beyond the coronal suture. The outer table of the skull remains unaltered, but the diploe appears to be diminished or obliterated, according to the degree of hyperostosis. The process differs, roentgenographically at least, from other involvements of bone in that there is no porosity or loss of calcium, so that it is reasonable to suppose that it is a disorder of calcium metabolism in which that mineral is presented in excess in the body. In spite of the different degrees or types of the disorder, the cases have an astonishing similarity to each other and vary only in the intensity of the symptoms. Thus far, only hypotheses as to the cause of the process have been advanced. The disease will be found with far greater frequency when it is sought for by roentgenologists as a routine. The descriptive name at present employed for the syndrome suffers from the drawback inherent in using a single feature of a disorder to designate the whole. The hyperostosis, while the surest sign of the disease, may be the least important of its manifestations.

HUNTER, Portland, Ore. [ARCH. PATH.]

CEREBRAL SYPHILIS AND GLIOMA. J. DE BUSSCHER and H. J. SCHERER, J. belge de neurol. et de psychiat. **35**:714 (Dec.) 1935.

The authors report the case of a patient with glioblastoma multiforme and syphilitic meningitis. They make the statement that tumor of the brain may exist in patients with syphilis of the central nervous system and that often a complete anamnesis will aid in differentiating the symptoms due to the two conditions. They believe that positive serologic findings do not contraindicate surgical procedure and that in conditions which are not too far advanced the treatment of choice consists of surgical intervention followed by energetic medical treatment.

WAGGONER, Ann Arbor, Mich.

DIFFERENTIAL DIAGNOSIS OF TUMOR OF THE BRAIN AND "PSEUDOTUMORAL" ENCEPHALITIS. J. DEREUX, J. belge de neurol. et de psychiat. **35**:729 (Dec.) 1935.

Dereux states that certain types of encephalitis may be mistaken for tumor of the brain. The difficulty of diagnosis is based on signs of localized cerebral damage, generalized signs or evidences of intracranial hypertension. He speaks of these inflammatory conditions as "pseudotumoral" encephalitis. These symptoms may occur in all types of encephalitis—that following infectious diseases, the toxic variety, von Economo's disease (encephalitis lethargica) or the encephalitides of the Baló or Heubner-Schilder type.

Dereux gives the following methods of differentiating encephalitis and tumor: 1. Localizing signs are more common in tumor. In encephalitis the signs are usually multiple, disseminated and transitory and are likely to exhibit advances

and remissions. 2. Generalized signs, such as fever and leukocytosis, are more likely to be present in encephalitis. While there are cases of encephalitis in which there is no elevation of temperature and cases of tumor accompanied by febrile reactions, a moderate febrile "grip incident" is more likely to precede the onset of encephalitis. 3. Signs of intracranial hypertension, such as papilledema and increased spinal fluid pressure, are more common in the group of tumors. 4. Roentgenologic signs may be the same in both tumors and encephalitis, but ventriculography may be of great value in the differentiation.

WAGGONER, Ann Arbor, Mich.

VON HIPPEL'S DISEASE; LINDAU'S DISEASE. H. VIALLEFONT, Rev. d'oto-neuro-opht. **13**:405 (June) 1935.

Viallefont has collected all that has been published on this disease. The name von Hippel's disease is applied in cases of isolated angiomatosis of the retina, while Lindau's disease is reserved for cases of retinal angiomatosis associated with angioma of the nervous system and with visceral malformations. These diseases are compared with Bourneville's disease, Recklinghausen's disease and the encephalotrigeminal angiomatosis of Crouzon. Von Hippel published his observations in 1926, and in 1927 Lindau called attention to the coincidence of retinal angiomatosis and cyst of the cerebellum. The evidence shows that the condition is not local but is a malformation of vascular tissue involving the central nervous system, the retina and even all organs of the body. Its hereditary and familial character is emphasized. Cushing and Bailey were the first to diagnose Lindau's disease clinically. The close relationship of Lindau's disease, Bourneville's disease (tuberous sclerosis of the cerebral convolutions), encephalotrigeminal angiomatosis, Recklinghausen's disease and phacomatosis of van der Hoeve is pointed out. The familial character of this whole group of diseases has been demonstrated by Ley, van Bouwdijk, Bastiaanse, van Bogaert, Guillain and Lagrange, Bielschowsky, van der Hoeve and Nieuwenhuyse. Embryologically, there is a close relation between the branches of the trigeminal nerve and the vascular trunks from the internal carotid artery. It is therefore easy to conceive of localization of angiomatous formations both in the skin and in the meningeal territory of the trigeminus nerve. Oppenheim observed a child with nevus of the face, convulsive crises and three round tumors of the retina.

DENNIS, San Diego, Calif.

ARACHNOIDITIS OF THE BASE OF THE BRAIN. H. BOURGEOIS and others, Rev. d'oto-neuro-opht. **14**:323 (May); 385 (June) 1936.

This article is a report to the ninth congress of the Sociétés d'Oto-neuro-ophtalmologie in May 1936 and was prepared by men representing otology, neurology, ophthalmology and neurosurgery. The subject is discussed exhaustively in an introduction, twelve chapters and a bibliography.

Arachnoiditis of the middle fossa, observed by neurologists and oculists, and that of the posterior fossa, observed by otologists, appear to be different diseases. The differences are more apparent than real and represent only different stages of the same pathologic process. Anterior to a line represented by the superior borders of the two petrous pyramids the disease tends to be plastic and fibrous, and posterior to this line, serous and cystic. The lesion responsible for both forms is alteration of the soft meninges, followed by accumulation of liquid. Much confusion in the descriptions of arachnoiditis arises from the fact that neurologists and neurosurgeons, on the one hand, and otologists, on the other, have not described the same clinical entity because they have observed different types of the condition. The otologist more frequently encounters circumscribed serous meningitis, which is the primary reactional type, while the neurologist and the neurosurgeon see especially cases of superacute or chronic evolution, either global syndromes of hypertension or localized syndromes of compression (pseudotumor).

The evolution of the disease is slow, with symptomatology characteristic of localized pseudotumor; hypertension is a secondary phenomenon. Exciting causes are neurotropic or generalized infection and infection of the accessory sinuses. Adhesions form, and the endothelium becomes irritated, resulting in hypersecretion and the formation of cysts. They occur on the convexity, in the region of the optic chiasm and at various points in the posterior fossa. In the posterior fossa the evolution is complicated by anatomic and physiologic conditions. The following forms of arachnoiditis are described: arachnoiditis of the chiasmic region, localized arachnoiditis of the posterior fossa, obstructive hydrocephalus arising from arachnoiditis around the openings of Luschka and Magendie, the syndrome of hydrocephalus of the posterior fossa with local arachnoiditis and multiple localizations.

Whatever its location, arachnoiditis is characterized by thickening and adhesions of the membrane or cystic formation or both. The subjacent tissue always participates in the inflammatory process. In the chiasmic region a third form may occur: the atrophic. In the posterior fossa the form most often seen by the otologist is represented by a large collection of fluid, which is usually discovered during the course of exploration of the cerebellum for abscess. As soon as the dura is opened, there is escape of fluid, and the patient recovers without further measures. These large cysts are located in some part of the cerebellomedullary cistern; the small cysts are scattered through the adherent arachnoid and occur mostly on the posterior face of the pyramid. The dura may be either unchanged or thickened, soft and fluctuating. The limited fibrous type is much less frequent. The fibrous bands sheathe and compress the nerve trunks, as in the chiasmic form. When such lesions are located in the roof of the fourth ventricle, obstructive hydrocephalus is produced by blocking the foramina of Lushka and Magendie or the aqueduct of Sylvius. Still another type is diffuse hydrops of the posterior fossa, with arachnoiditis. Closure of the foramen ovale of Pacchioni explains the limitation of hydrocephalus to the posterior fossa. After evacuation of the fluid, the cerebellum is seen to be edematous, and veils of inflamed arachnoid cover various cranial nerves.

Arachnoiditis occurs most often between the ages of 20 and 40 years and is more common in the male. Lesions in the posterior fossa most often accompany or follow infection of the ear. Four etiologic factors are involved in arachnoiditis: infection of the cavities of the skull, traumatism and neurotropic and general infection. Inflammation of the fronto-ethmoid cells and, especially, of the sphenoid cavity is frequently the cause of arachnoiditis in the middle fossa. The propagation of neurotropic infection to the arachnoid is by way of the perivascular lymph spaces which drain into the arachnoid spaces. The rich blood supply of the arachnoid facilitates its involvement in general infection. Traumatism acts by direct destruction, by production of hematoma, by irritation from toxic products of degeneration of the focus or by direct infection from the cavities of the skull when the trauma opens a communication between them and the arachnoid. In the course of otitis, the pathways of infection are the bone (osteitis or preformed pathways), the veins and venous sinuses and the lymphatic sheaths of the nerves. The lymphatic pathways are not now believed to be important factors, except in cases of arachnoiditis of the middle and anterior fossae arising from propagation of infection in the nose, nasal sinuses and pharynx. The reaction of the arachnoid to local infection is: (1) exudation due to irritation of its endothelium; (2) destruction of the endothelium in places, resulting in the formation of adhesions, which isolate areas of intact endothelium, and (3) exudation and the formation of cysts. The adjacent nerve structure shares in the infection and becomes compressed by the adhesions and cysts. Edema occurs through venous and arterial compression. The choroid plexuses react to irritation from infection or the toxic products of disintegration by overproduction of fluid.

Chiasmic arachnoiditis is first manifested by visual difficulties, which may be of all degrees. The ophthalmoscopic signs correspond to the different modifications of the papilla: stasis, papillitis or complete atrophy. Other appropriate signs

indicate involvement of neighboring organs. Changes in the visual fields are the most important: concentric narrowing for white and colors, central scotoma and the various forms of hemianopia. Central scotoma and partial hemianopia are the most characteristic findings. Paralysis of the third or sixth nerve sometimes occurs. Symptoms of infundibulohypophysial involvement have been observed.

In the posterior fossa three forms of arachnoiditis are described: (1) limited areas of adhesions or cysts (localized arachnoiditis); (2) adhesive lesions located at the fourth ventricle (obstructive hydrocephalus due to arachnoiditis) and (3) distention of the entire posterior fossa or of the great cistern only by fluid under pressure. In all forms the evolution distinguishes the clinical picture from that of true tumor. A history of chronic otitis is frequent. Arachnoiditis localized in the internal auditory meatus closely resembles that in the posterior fossa and is essentially isolated neuritis of the eighth nerve.

Precerebellar arachnoiditis is comparatively rare. It is characterized by disturbance in equilibrium, a tendency to fall toward the diseased side or backward, nystagmus to the diseased side and intense vertigo. Signs and symptoms of meningeal and pyramidal involvement are absent. There is failure to react to the caloric test and to that for provoked vertigo; labyrinthine hypo-excitability is revealed by the turning test. Vestibular disturbances are accounted for by pressure from the cystic arachnoid on the endolymphatic sac, causing edema of the labyrinth. Fever, emaciation and signs of hypertension follow. Differentiation from cerebellar abscess is almost impossible. If on exploration no abscess is observed, the posterior face of the petrous pyramid must be examined for arachnoid cysts. Prepontile arachnoiditis is distinguished by the contrast between the paucity of kinetic signs of cerebellar involvement and the violence of the disequilibrium.

Laterobulbar arachnoiditis begins with torticollis and limitation of the movements of the head, which are soon followed by paralysis of the palate and tongue, signs of hypertension and a unilateral cerebellar syndrome. Arachnoiditis of the posterior lacerated foramen gives rise to the syndrome of Vernet: simultaneous involvement of the pneumogastric, glossopharyngeal and spinal accessory nerves.

In the syndrome of hydrocephalus arising from arachnoiditis of the foramina of Luschka and Magendie, signs of ventricular blockage and hypertension dominate the picture. The initial symptoms appear some time after infection and consist of signs of progressively developing hypertension. A psychic syndrome next appears and is characterized by intellectual enfeeblement, spatial disorientation and confusion, or even dementia with sexual excitation.

Two forms of hydrocephalus of the posterior fossa with arachnoiditis are recognized: generalized hydrops and hydrops limited to the cisterna magna. Hydrops of the cisterna cerebellomedullaris resembles clinically that of the cisterna magna but is distinguished by special attitudes of the neck. At onset few neurologic signs can be elicited. Exophthalmos and papillary stasis are most commonly observed. In the manifest stage the hypertension becomes permanent, and mental confusion or moria with a cataleptoid attitude occurs. Hyperextension or hyperflexion of the neck is present. Disequilibrium, with a tendency to fall backward, is marked, but kinetic motility is intact. Tonic crises (cerebellar fits) complicate the scene; signs of bulbar involvement appear; the pulse is slowed, and respiration is disturbed (Cheyne-Stokes type). If the crisis is prolonged, death from bulbar involvement is imminent. Radicular disturbances occur late and involve the fifth, seventh and eighth nerves. Cochleovestibular lesions are discrete, disharmonious and dissociated. Lumbar puncture is especially dangerous. Examination of the spinal fluid shows slight hypertension and hyperalbuminosis with cytologic dissociation. Encephalography is dangerous. The evolution is similar to that of hydrops of the posterior fossa, but death may occur at any time during the tonic crises.

When there is no preexisting otitis, the differential diagnosis of arachnoiditis of the posterior fossa and tumor of the brain is the most important. The question

is complicated by the fact that secondary arachnoiditis may accompany tumor. Vincent's precept is that the diagnosis of arachnoiditis should not be made until the whole region of the seventh, eighth and ninth nerves has been inspected, without observation of a tumor. According to de Martel, variability of the signs points rather to arachnoiditis. Berdet's dictum is that reliance should be placed on the nuances in the entire clinical picture: presence of infection in the cavities of the skull, signs of encephalitis, optic neuritis, slight general infectious processes, slight discordances in the symptomatology and evolution in repeated exacerbations. The syndrome of hydrops of the great cistern and tumor of the midline differ in that the symptoms in the former are more stormy; the evolution is more rapid, and the vestibular disharmony is more accentuated.

When there is preexisting otitis, labyrinthitis without intracranial complication, otitic cerebellar abscess and acute otitic hydrocephalus must be considered in differential diagnosis. Pure labyrinthitis does not show dissociation of the functional signs, and vestibular examination reveals consistent reactions. Vertigo is clearly lateralized, and tinnitus accompanies the symptoms. The signs of cerebellar abscess and those of hydrops of the posterior fossa are similar. Careful consideration of the etiologic factors, the mode of onset and the course will help in differentiation. Arachnoiditis is more likely to develop in the course of apparently benign otitis; its onset is sudden; the temperature is higher and the pulse more rapid; headache seems more superficial; the general condition of the patient is not so profoundly affected; vertigo when present is more violent, and in general the cerebrospinal fluid is unchanged.

A number of cases of arachnoiditis with multiple localization have been reported. Irregularity in evolution and variability in the symptoms are the most characteristic signs. Ventriculography often shows ventricles which are small and in place (arachnoiditis of the convexity), normal but slightly deformed ventricles (arachnoiditis of the optic chiasm) or dilated and symmetrical ventricles, with or without block of the ventricles (arachnoiditis of the posterior fossa). Encephalography is too dangerous to be used. Generalized serous meningitis is in fact encephalo-arachnoiditis. It may be acute or subacute and may require decompression, but it lacks the chronicity and variability of localized arachnoiditis. A striking feature is the absence of signs of localization, even in the presence of signs of global hypertension. It would be difficult to distinguish the condition known as "large brain" (*Hirnschwellung* of Virchow); both conditions may be caused by a neurotropic virus. Ventriculography reveals very small ventricles. Encephalitis arising from a neurotropic virus may cause symptoms of false compression, but these symptoms are due to accompanying arachnoiditis.

The surgical treatment of arachnoiditis is concerned first with the removal of the infectious foci thought to be responsible for the condition. Puncture of the dura in front of the sigmoid sinus for relief of arachnoiditis of the cerebellar region following mastoiditis should be undertaken with care, but is practically without danger and is efficacious in most cases. Perhaps more to be recommended is the approach from behind the sinus, as in Dandy's method for section of the eighth nerve. The treatment of chiasmic arachnoiditis is medical, surgical and roentgenologic. Surgical intervention should be practiced at the proper moment, while there is still the maximum chance of success and before blindness or papillary atrophy has occurred. In about two fifths of the cases the Wassermann reaction is positive. Indications for operation are: (1) regular failure of visual acuity, (2) progressive narrowing of the visual fields or increase in the central scotoma and (3) edema and atrophy of the papilla, continuing in spite of other remedial measures. When diffuse serous meningitis or cerebral edema is present, subtemporal decompression should also be performed. The after-treatment consists of treatment for the causal factor and, when this is not known, of a series of alternate treatments with mercuric cyanide and iodine. In the years following, a series of applications of semipenetrating roentgen rays are advocated. The results of operation are good in half the cases.

DENNIS, San Diego, Calif.

SYMPTOMATOLOGY OF DISORDERS OF THE FRONTAL LOBE. J. GERSTMANN, Monatschr. f. Psychiat. u. Neurol. **93**:102 (April) 1936.

Gerstmann describes a hitherto unreported symptom of disease of the frontal lobe, namely, spontaneous turning of the body. It has been observed chiefly in patients with tumor of the frontal lobe who, as a rule, showed other motor symptoms, such as ataxia due to disease of the frontal lobes. The turning movements appear only when the patient is upright and are especially likely to occur when the feet are close together. The patient turns in circles of varying radius, moving toward the side on which the lesion is located. The movements resemble voluntary actions but are involuntary and compulsive. They are frequently associated with disturbance of equilibrium, which shows itself in a tendency for the patient to fall to the side contralateral to the lesion. Occasionally turning about the long axis of the body occurs. Like other motor symptoms of disease of the frontal lobe, these turning movements may be absent, even in cases in which involvement is severe. Furthermore, they may be much less outspoken at one time than another and may therefore be overlooked unless repeated examinations are made.

ROTHSCHILD, Foxborough, Mass.

## Diseases of the Spinal Cord

ABNORMALITIES OF MICTURITION DUE TO SYPHILIS OF THE NERVOUS SYSTEM. O. R. LANGWORTHY, J. E. DEES and L. G. LEWIS, Am. J. Syph., Gonor. & Ven. Dis. **20**:364 (July) 1936.

Since vesical infection is the commonest cause of death among patients with tabes, the understanding and management of urinary abnormalities are of major clinical importance. The concept of "cord bladder" is an oversimplification, for there are many types of disturbance of the bladder due to injury to the cord. While most of these are associated with tabes, some occur in connection with syphilitic spastic paraplegias, while others spring from thrombosis of the spinal arteries or from meningomyelitis. Examination of the histories in 278 cases of tabes showed abnormalities of micturition in 50 per cent. Owing to injury of the sensory fibers the patient is unaware of distention of the bladder and allows the organ to be stretched, to the detriment of its muscular tone. This in turn results in slowness in initiating micturition and diminution of expulsive force. Graphic records indicate that the chief abnormality is inability to initiate and sustain vesical contractions strong enough to empty the bladder. Cystoscopic examination in cases of tabes discloses fine trabeculations of the bladder, spreading from the lateral edges of the trigon into the wall. They are evenly set with shallow interstices. This condition can be seen early in the disease and may indicate the tabetic condition before other signs of the disorder.

Langworthy, Dees and Lewis disapprove of emptying the residual urine by catheterization in tabetic patients who have no infection of the bladder, believing that instrumentation almost inevitably produces cystitis. In the early stages antisyphilitic therapy should be vigorous, for this often relieves the patient. To prevent further stretching of the vesical wall, the patients should be instructed to empty the bladder at regular intervals of four hours regardless of how full the organ seems. They should also learn by practice how to stop and start the urinary stream at will. Sympathectomy offers some hope for patients with early tabes whose vesical symptoms have not responded to antisyphilitic treatment.

DAVIDSON, Newark, N. J.

MENINGITIS SEROSA CIRCUMSCRIPTA SPINALIS (SPINAL ARACHNOIDITIS). J. ST. C. ELKINGTON, Brain **59**:181, 1936.

Localized collections of fluid under tension in the pia-arachnoid, giving rise to symptoms of spinal compression, were described by Spiller, Musser and Martin in 1903. Since, numerous contributions to the subject have appeared in the litera-

ture under many different titles. Postmortem material is scanty, and detailed descriptions of the pathologic changes are confined to papers by Grinker (1926) and Marinesco (1934). The present paper consists of an analysis of the symptoms and signs observed in forty-one cases of what Elkington terms "meningitis serosa circumscripta spinalis."

From an etiologic point of view, the disease occurs preponderantly in males during middle life. Analysis in the present series of cases confirms the inference that various conditions are capable of initiating a similar process in the spinal meninges and that there is, in fact, no single cause for the disease. A history of spinal injury was obtained in nine cases, of syphilis in four, of meningococcic meningitis in two, of gonorrhea in four and of other systemic infections in six. In the remaining cases no cause was traced. Horsley (1909) suggested that syphilis and gonorrhea are responsible and that trauma plays no part; Mauss and Krüger (1918) reported in detail fifty-four cases in which the onset followed a war injury. Others have regarded the disease as the consequence of various systemic infections, and Bouché (1914) specifically mentioned typhoid. Association with tuberculosis and arthritis of the spine was mentioned by Vincent (1930). Several cases have been recorded in which the disease followed meningococcic meningitis (Batten, 1916; Guillain, 1932). Kron (1927) reported a case in which the disease appeared after a septic abortion.

The clinical picture presented by the disease is variable. Any part of the spinal cord or cauda equina may be affected; the process may be either strictly localized or diffuse, and the onset may be rapid or gradual. Although no portion of the spinal cord is immune to the disorder, the dorsal portion is most often involved and the upper part of this region more often than the lower. Two modes of onset are commonly encountered, viz., spontaneous pain and symptoms of spinal compression. The pain usually begins on one side of the body but later becomes bilateral. At first it is commonly confined to the cutaneous distribution of one or two spinal segments but usually spreads until a wide cutaneous area is involved, differing in this respect from the root pain experienced in spinal compression from other causes. Whether the mode of onset is rapid or gradual, examination of the patient usually shows well defined motor, sensory and reflex signs of local disease of the spinal cord and its nerve roots. Sphincter disturbances are mild as compared with the severity of the motor and sensory changes. Cutaneous lesions and bed sores are strikingly rare.

The Wassermann reaction of the blood was weakly positive in one case. Complete block on manometric examination was found in one case and partial block in two of six cases examined. Moderate pleocytosis has been reported by some investigators, but the majority of reports in the literature show absence of any increase of cells in the spinal fluid. All authors have found the Wassermann reaction of the cerebrospinal fluid uniformly negative. Elkington's findings are in accord with these reports. Determination of the total protein content of the spinal fluid revealed a gross excess in five of twenty-one cases. In all these instances there was other evidence of loculation, and it seems, therefore, that in meningitis serosa circumscripta spinalis marked increase in protein occurs only as a result of occlusion of the subarachnoid space. Of thirteen cases in which the Lange colloidal gold test was carried out the reaction was abnormal in one, in which a meningitic curve was obtained.

Barré (1925), Hiller (1926-28), Moniz (1933), Marinesco (1934) and Paulian and Turnesco (1933) drew attention to the striking features presented in roentgenograms of the spine in cases of meningitis serosa circumscripta after the introduction of iodized poppy-seed oil into the cisterna magna. While in cases of spinal compression from other causes the opaque oil is held in its entirety at the level of the spinal lesion, these authors found that in the presence of diffuse arachnoid adhesions the oil is arrested in droplets over a considerable extent above the site of the main lesion, giving an appearance reminiscent of a guttering candle. At the same time, the arrest is incomplete, and some of the oil is seen in the sacral end of the subarachnoid space. In the present series iodized oil was introduced into

the cisterna magna in seven cases. In five of these it was arrested at a single level, which in each case was observed at operation to be the site of marked abnormality of the subarachnoid space. In two cases the oil descended normally to the bottom of the subarachnoid space. The diffuse arrest referred to in the literature was not seen.

While the diagnosis of meningitis serosa circumscripta spinalis can only be suspected, and cannot be definitely established before operation, there are certain features of the disease which raise the possibility of clinical diagnosis. The disease is predominantly one of middle age, and a history of definite spinal trauma, of past infection of the subarachnoid space or of syphilis is of value. Though the more common mode of onset is that of insidious spinal compression, the commencement with spontaneous pain, when it occurs, is highly suggestive. The pain may be of sudden onset, is usually intense and intractable and is diffuse in distribution and frequently associated with hyperesthesia. Usually these are signs of localized spinal compression, together with more diffuse involvement of the spinal nerve roots. The root symptoms tend to be more conspicuous than those associated with spinal tumor, whereas the spinal compression is slow in reaching an extreme degree, so that trophic changes and disturbance of the sphincters are long delayed. The diffuse, patchy arrest of iodized oil over a wide area of the subarachnoid space is suggestive of widespread adhesions in the subarachnoid space. This appearance, however, may be absent in cases of meningitis serosa circumscripta. Furthermore, spinal tumor, especially the vascular type, is frequently associated with arachnoid adhesions above and below the lesion.

At operation it is commonly observed that the dura mater pulsates defectively and that the arachnoid is thickened and bound by adhesions to the overlying dura and, more often still, to the underlying pia. These arachnoid adhesions are in some instances associated with solitary or multiple cysts, which in turn compress the cord. Further, the adhesions often disturb the normal vascular arrangement of the cord; in such cases the cord appears pale and shrunken. Consideration of the observations at operation and of the pathologic material available in the author's cases and from the descriptions in the literature leaves little doubt that the essential change in meningitis serosa circumscripta is a morbid process in the spinal leptomeninges, whereby abnormal adhesions and bands are formed in the subarachnoid space, which may or may not be associated with cystic accumulation of fluid in the meshes. These adhesions owe existence to a low grade inflammatory process, which is probably of diverse origin. They vary in degree from single bands and diffuse fine strands of fibrous tissue to dense adhesions obliterating the subarachnoid space and enveloping the emerging nerve roots. From whatever cause the meningeal adhesions arise, they produce symptoms by disturbing the functions of the spinal cord or its nerve roots by direct mechanical pressure and by interference with the vascular supply of the cord, which leads in its turn to intramedullary changes.

The prognosis is dependent on the length of time that the disease has existed before operation and the extent of irreversible damage to the cord. The patients in the author's series that did well after operation were found to have had a short preoperative history; in none of them was there described any abnormality of the cord itself at the time of operation.

SALL, Philadelphia.

TWO ANATOMOCLINICAL OBSERVATIONS OF LANDRY'S PARALYSIS. P. CALLEWEART, J. belge de neurol. et de psychiat. **36**:368 (June) 1936.

Calleweart describes two cases of Landry's paralysis, in each of which the disease followed a rapid course and resulted in death in less than four days. In both instances the febrile reaction and the meningeal irritation were insignificant, and in neither were there definite abnormalities in the cerebrospinal fluid. The disease in one case showed ascending motor involvement, with hypotonia and loss of reflexes, and resembled poliomyelitis. In the other it was manifested by motor difficulties accompanied by sensory changes, but without pain; the clinical signs suggested transverse myelitis. In both cases congestion of the cord and meninges was shown, with minute hemorrhagic foci. The inflammatory reaction was less

than one would expect. In one case there was intense chromatolysis of the cells of the anterior horns, with moderate leukocytic infiltration. In the other involvement of both the posterior and the lateral columns was shown, with a large zone of necrosis in the lower cervical region, which involved both the white matter and the anterior horns.

Calleweart calls attention to the diversity of opinion concerning the cause of lesions in Landry's paralysis. When the condition was first described, it was considered to be a specific disease characterized by the absence of lesions in the nervous system. This opinion may have arisen because of the lack of technical facilities at the time, but cases are still reported in which no lesions are observed. Neuritic forms of the disease have been described. Marie and Tretiakoff have classified Landry's paralysis into the poliomyelitic, the leukomyelitic and the diffuse ascending myelitic form. It is usually possible to distinguish the neuritic and the myelitic variety, but the two lesions may coexist in the same case. Suggestions as to etiology are as numerous as the classifications of the condition. The disease is often diagnosed as transverse myelitis. It may be related to poliomyelitis, as cases may occur during epidemics of infantile paralysis. The syndrome may follow a great number of infectious diseases and intoxications; disturbances diagnosed as Landry's paralysis have occurred in association with malaria, typhoid, measles, smallpox, diphtheria, tuberculosis and syphilis. Conditions described as Landry's paralysis have in some instances terminated multiple sclerosis. Calleweart believes that Landry's paralysis is not due to a single etiologic agent and that the forms may differ somewhat clinically, although all fall into the classification of Marie. He classifies the condition in his two cases as the "degenerative poliomyelitic variety" and the "diffuse degenerative ascending myelitic variety," both of which illustrate the variations which may occur in the clinical manifestations of acute ascending myelitis.

WAGGONER, Ann Arbor, Mich.

CHANGES IN THE SPINAL CORD AND POSTERIOR ROOT GANGLIONS IN SEPSIS. S. S. WAIL, Virchows Arch. f. path. Anat. **295**:414, 1935.

The spinal cord and posterior root ganglia were examined histologically in thirty cases of fatal sepsis. Swelling of the walls of small blood vessels, sometimes with thrombus formation, fibrinoid necrosis, perivascular cellular proliferation and hemorrhage were observed. Wail considers the changes hyperergic.

SCHULTZ, Evanston, Ill. [ARCH. PATH.]

## Vegetative and Endocrine Systems

BIOLOGIC EFFECTS OF THYMUS EXTRACT (HANSON). L. G. ROWNTREE, J. H. CLARK, A. M. HANSON and ARTHUR STEINBERG, Arch. Int. Med. **56**:1 (July) 1935.

The continuous administration of Hanson's thymus extract produced an acceleration in the rate of growth and development in successive generations of white rats. The thymus glands of calves from 2 to 6 weeks old were extracted in a 0.5 per cent solution of hydrochloric acid with heat. Daily injections of 1 cc. of the extract were administered intraperitoneally to six rats in a colony of twelve. The other six and their descendants served as controls. Descendants of the tested group were also treated with thymus extract and mated; their offspring were treated with the extract and mated again. In this way the remote effect of continuous and interrupted administration of thymus extract could be studied.

The families treated with thymus extract showed an acceleration in almost all developmental modalities, e. g., size of litter, weight, growth, age of opening the ears and time of eruption of the incisor teeth. If the treatment was maintained uninterruptedly through successive generations, the acceleration was cumulative. If the treatment was interrupted for one generation, the effects of the administra-

tion of the extract to the prior generation were nullified. The rats treated with thymus extract were larger and more mature than their untreated cousins and appeared more healthy and more contented. No interpretation of this experiment in terms of the function of the thymus is made by the authors, although the striking growth-stimulating potentialities of the gland are stressed.

DAVIDSON, Newark, N. J.

QUANTITATIVE STUDIES ON THE STRUCTURAL CHANGES INDUCED IN THE ANTERIOR HYPOPHYSIS BY INJECTIONS OF OESTRIN. J. M. WOLFE and C. S. CHADWICK, Endocrinology **20**:503 (July) 1936.

Injection of an estrogenic substance or implantation of ovarian tissue into castrated female rats resulted in either the prevention or the production of regression of changes in the anterior lobe of the pituitary gland, following castration. Injection of sufficient amounts of an estrogenic substance induced changes in the anterior lobe comparable to those of pregnancy. In this paper are presented quantitative data on the anterior lobe of the pituitary in three groups of female rats.

Two groups of immature female rats (a total of seventeen animals) received injections of 10 and 200 rat units, respectively, of an estrogenic substance for five days; eleven litter mates served as controls. In rats receiving 10 rat units daily there were moderate basophilic degranulation and loss of granules in relatively few eosinophils. In rats receiving 200 rat units degranulation of both the basophils and the eosinophils was more evident.

In a second series, two groups of rats (a total of fifty-two animals) received daily injections of 10 and 200 rat units, respectively, of an estrogenic substance for ten days; nineteen litter mates served as controls. In rats receiving 10 rat units daily practically all the basophils and moderate numbers of the eosinophils were degranulated. In rats receiving 200 rat units the basophilic degranulation was complete, and many eosinophils showed loss of granules.

In a third series, two groups (a total of thirty-nine animals) received a single injection of 10 and 200 rat units, respectively, of an estrogenic substance. Various members of these two groups were killed from one to five days after injection. Nineteen litter mates were used as controls. Single injections of 10 rat units induced more extensive degranulation of the basophils and loss of granules in a few eosinophils in the rats killed four and five days after injection.

Differential cell counts were made on all the sections studied. The relative percentages and the mean numbers of the various cell types counted per section were calculated. Quantitative data are presented statistically. The pituitary glands of rats receiving injections of an estrogenic substance were increased in weight, as compared with those of the litter mates used as controls. The degree of this increase in weight was proportional to the amount of the estrogenic substance injected and the length of the experimental period.

PALMER, Philadelphia.

THE RELATIONSHIP OF THE ANTERIOR PITUITARY GLAND TO THE THYROID AND OVARY. LEO LOEB, JOHN SAXTON and S. J. HAYWARD, Endocrinology **20**:511 (July) 1936.

It has been demonstrated that extracts of anterior pituitary from cattle produce corpora lutea or similar structures in the ovary and cause the growth and maturation of follicles. Rats and mice, which served as test animals in these investigations, responded in a different fashion from that of the guinea-pigs, in which all similar extracts caused a remarkable transformation of the thyroid gland. The authors' method of investigating the effect of anterior pituitary on the thyroid and ovary consisted in immersion of the anterior pituitary glands, irrespective of size, in various solutions and in subsequent implantation of the glands into the test animals, primarily guinea-pigs. It can be shown that, as a result

of this preliminary treatment, the pituitary gland undergoes definite changes which can be demonstrated through the effect on the thyroid and the ovary after implantation. By this method the relationships between the "ovarian hormones" and the thyroid-stimulating hormone of the anterior lobe of the pituitary can be studied.

It was found that there exists a substance in the anterior lobe of the pituitary, mainly of cattle, sheep and pigs, which causes rapid destruction of follicles in the ovary of the guinea-pig. There are indications that extracts which contain this substance may be obtained in effective concentration from the glands of cattle, while the thyroid-stimulating and the luteinizing substances are present only in very small amounts. This follicle-destroying substance may be designated as "atresin."

While, as a rule, the thyroid-stimulating hormone is found in association with the luteinizing hormone and with "atresin" and while its occurrence shows an inverse relation to that of the hormone causing growth and maturation of follicles, it is possible experimentally to separate these three substances. Thyroid-stimulating hormone present in the anterior lobe of the pituitary in certain persons (puerperal women and children before puberty) may also be associated almost entirely with the hormone producing follicular growth and maturation; the same combination was observed in some human glands that were treated with solutions of alcohol saturated with sodium sulfate. On the other hand, it can be shown experimentally that the luteinizing hormone may be active without any indication of the presence of thyroid-stimulating hormone. It is therefore concluded that all these hormones may act independently of each other.

PALMER, Philadelphia.

INTERRELATIONSHIPS AMONG URINARY, PITUITARY AND PLACENTAL GONADOTROPIC FACTORS. J. B. COLLIP, J. A. M. A. **104**:556 (Feb. 16) 1935.

Collip confines his discussion to the known estrogenic and gonadotropic factors of the pituitary gland, placenta and urine. A great mass of factual evidence bearing on these active principles has been accumulating within the past few years and indeed is still being added to rapidly month by month. Proved facts must be accepted, but an adequate and totally satisfactory correlation of these facts is quite impossible at this time. The author hopes only to present a point of view that seems the most satisfactory explanation of the known facts. He considers the active principles, the estrogenic substances without gonadotropic effect, the gonadotropic principles and the influence of the gonadotropic hormones on the ovary.

A CHANGE IN THE BASOPHIL CELLS OF THE PITUITARY GLAND IN COMMON TO CONDITIONS WHICH EXHIBIT THE SYNDROME ATTRIBUTED TO BASOPHIL ADENOMA. A. C. CROOKE, J. Path. & Bact. **41**:339, 1935.

A hyaline change in the basophilic cells of the pituitary gland is described which appears to be an expression not of cell degeneration in the ordinary sense but probably of altered physiologic activity. The hyalin was observed in slight amount in a few basophilic cells of the anterior lobe in only nine of about three hundred and fifty pituitary glands of persons with various conditions in which the syndrome attributed to basophil adenoma was absent. Its presence in examples of the different conditions in which it was present was inconstant and exceptional. It was observed in large amount in many basophilic cells in the acini of the anterior lobe in all twelve available examples of the syndrome attributed to basophilic adenoma, a neoplasm of the thymus or a neoplasm or hyperplasia of the adrenal cortex. Analysis shows that this conspicuous amount of hyaline change was the only abnormality common to all twelve examples of the syndrome, and it is concluded that it is the abnormality of fundamental significance.

FROM THE AUTHOR'S SUMMARY [ARCH. PATH.].

THE EFFECT OF PITUITARY (POSTERIOR LOBE) EXTRACT UPON THE URINARY FLOW. ADLI SAMAAN, J. Physiol. **84**:54P (July 24) 1935.

Motzfeld in 1917 stated that the antidiuretic effect of posterior pituitary extract is abolished after the elimination of renal innervation. Samaan reports that observations on unanesthetized bitches show that the "antidiuretic threshold dose of the extract" (the intravenous dose which produces the smallest reduction of urine in an animal with uniformly maintained water diuresis) is remarkably constant in any one bitch and is unchanged after renal denervation. With larger doses the inhibition of urine of the denervated kidney is as marked as that of the normal kidney, or sometimes even more so. The intravenous administration of the extract in dogs (normal or with denervated kidneys) ingesting dilute solutions of urea (from 1 to 2.5 Gm. per hundred cubic centimeters) or of sodium chloride is followed by a reduction of urine, the degree and duration of which are relative to the dose given. On the other hand, diuresis produced by ingesting stronger solutions of urea (from 8.3 to 10 Gm.) is unaffected by doses two thousand times as great as the antidiuretic threshold dose. ALPERS, Philadelphia.

THE RESPONSES OF NORMAL AND HYPOPHYSECTOMIZED RABBITS TO ADRENALINE. C. BACHMAN and G. TOBY, J. Physiol. **87**:1 (June 10) 1936.

Bachman and Toby examined the hyperglycemic responses to epinephrine in hypophysectomized rabbits. In the intact rabbit, both in that which is fed and that which fasts for forty-eight hours, there is marked hyperglycemia after the subcutaneous injection of 0.25 mg. of epinephrine per kilogram of body weight. The stores of glycogen are maintained presumably either by new formation of carbohydrate within the liver or by transference of carbohydrate from the muscle in the form of lactic acid. The degree of hyperglycemia observed is dependent largely on the amount of glycogen initially present in the liver. The hypophysectomized rabbits which are fed react irregularly to epinephrine but may exhibit marked hyperglycemia, provided that the stores of glycogen in the liver are ample. Animals which have fasted for only fifteen hours, however, have little glycogen in the liver and show little hyperglycemic response to epinephrine. The hypophysectomized animals retain considerable amounts of glycogen in the muscles throughout a short fast, yet respond poorly to epinephrine.

In the intact rabbit an important part of the material for hyperglycemic reactions to epinephrine administered subcutaneously is supplied by the breakdown of glycogen in the muscles. Evidence is presented which suggests that impairment of hyperglycemic reactions to this hormone in the hypophysectomized rabbit may be due to the relative fixation of muscle glycogen. The authors believe that it is not unreasonable to assume that the muscle glycogen of completely hypophysectomized rabbits is not readily mobilized by epinephrine and that such animals fail to display epinephrine hyperglycemia principally because the liver is not constantly supplied with lactic acid derived from contraction of the muscles under the action of the hormone.

Accumulation of fat in the depots has been observed in hypophysectomized rabbits; it is seen also in castrated (but not in thyroidectomized) rabbits, which, however, respond normally to epinephrine.

There are no reliable estimates of the extent to which sugar which is newly formed from noncarbohydrate materials participates in epinephrine hyperglycemia. The possibility that inhibition of such glyconeogenesis is a cardinal consequence of hypophysectomy is not excluded. PALMER, Philadelphia.

MYXEDEMA, ACROMEGALY, INFUNDIBULOTUBERAL SYNDROME, MELANCHOLIC DELIRIUM, ONEIRISM, LIGNEOUS THYROIDITIS, PITUITARY ADENOMA AND PEDUNCULO-MESODIENCEPHALIC ENCEPHALITIS. L. MARCHAND, P. PETIT and J. FORTINEAU, Encéphale **31**:219, 1936.

A man aged 38 became hypochondriacal and easily fatigued after emotional shocks. Two years later repeated transitory edema with oliguria appeared. The following manifestations then appeared successively: loss of sexual activity;

asthenia; gain in weight (from 73 to 103 Kg.); polyphagia, polydipsia and polyuria; occipital headaches; vertigo; tinnitus; invincible somnolence; anxious melancholia, with ideas of persecution and self-accusation; auditory and visual hallucinations; agitation, and attempts at suicide. Examination showed: a dry, smooth, pale skin, which was scaly on the extremities; hypotrichosis; a broad tongue; thick lips; acromegaly; polycythemia; bradycardia, and cerebellar disturbances. The basal metabolic rate was minus 22 per cent. There was albuminuria. The cerebrospinal fluid was normal except for an increase in the total protein content. The eyegrounds were normal. Roentgen examination of the skull showed thickening of the calvarium and an unclear image of the posterior clinoid processes. Later the patellar and achilles reflexes disappeared; the patient grew weak on both sides, and a Babinski sign appeared on the left. The patient passed into coma and died, eleven years after onset of the illness. Autopsy showed ligneous thyroiditis, with dense fibrosis of the stroma and loss of most of the thyroid tissue. There were polymorphous changes in the glandular portion of the hypophysis, with fetal epithelioma (Roussy and Oberling), and hyperplasia, with adenomatous deviation of the cells, which contained no granulations. The brain showed adhesive leptomeningitis in places. The walls of the third ventricle, the midbrain and the medulla showed perivascular round cell infiltration, which was most marked about the floor of the fourth ventricle and the aqueduct. The diagnosis of myxedema was made only in retrospect, as its clinical manifestations were lost in the wealth of signs belonging to the diencephalic syndrome. Anxiety and melancholia have frequently been noted in connection with diencephalic lesions. The peculiar dream states with nocturnal hallucinations, recognized as such by the patient and consisting chiefly of bright, glistening objects, are in keeping with lesions near the sylvian aqueduct. The possibility that the encephalitic process, the nature of which could not be determined, also caused the changes in the pituitary gland is considered.

LIBER, New York.

OBSERVATION OF A NEW SYNDROME (BIEMOND) RESEMBLING THE LAURENCE-MOON-BARDET SYNDROME. A. DELHAYE and L. VAN BOGAERT, J. belge de neurol. et de psychiat. **36**:420 (July) 1936.

Biemond described a familial condition consisting essentially of infantilism of the hypopituitary type, coloboma of the iris, polydactyly, skeletal anomalies and mental retardation. He compared this symptom complex with the familial Laurence-Moon-Bardet syndrome. At autopsy Biemond observed a small pituitary gland, hydrocephalus with hydromyelia, a cerebral tumor and intestinal polyposis with carcinomatous degeneration of several of the tumors. Delhaye and van Bogaert report a similar case in which they made complete studies. The clinical characteristics were: obesity of the hypophysial type, with abnormal development of the skeleton, symmetrical brachydactyly, kyphosis, bilateral atypical coloboma genital hypoplasia, marked mental retardation, abnormalities in water and lipoid metabolism, eosinophilia, and a lowered basal metabolic rate. Four members of the family also showed some of these changes. The authors believe that this symptom complex can be differentiated from the Laurence-Moon-Bardet syndrome.

WAGGONER, Ann Arbor, Mich.

ENDOCRINE FACTOR IN THE PATHOGENESIS OF ARTERIAL HYPERTENSION, INCREASED INTRACRANIAL PRESSURE, AND PREMATURE ARTERIOSCLEROSIS. RÔLE OF THE HYPOPHYSIS. E. MERLE, G. PETIT and M. PRELLE, Rev. franç. d'endocrinol. **13**:173 (June) 1935.

Merle, Petit and Prelle report a clinical and anatomic study of a woman aged 45, who for a year was subject to paroxysmal attacks of arterial hypertension and showed signs and symptoms of increased intracranial pressure. She had several generalized convulsions and suffered from paroxysmal headaches and confusional states; she was subject to euphoric moods, stupor and somnolence. There were signs of asynergia of cerebellar origin and atrophy of the optic nerve. A few

weeks before death there developed left hemiplegia. Biochemical studies revealed hyperglycemia and hypercholesteremia. During the year of illness the patient became progressively cachectic. Autopsy revealed hypertrophy of the hypophysis, with lesions in the anterior lobe, hyperplasia of the cortex of the adrenal glands, hyperplasia of the thyroid gland and sclerotic changes in the ovaries. There was generalized atheromatosis, especially of the cerebral vessels. There were multiple small cerebral and cerebellar softenings, nephritic changes of the vascular type and hypertrophy of the left ventricle. The authors attempt to explain the complex pathologic picture on the basis of endocrine involvement. Invoking the clinical observations and the physiologic experiments of Cushing, Drouet and others, they come to the conclusion that the hypophysis has a regulatory effect on the arterial pressure either by direct hormonal action or by indirect influence on the diencephalic centers. The increased intracranial pressure is explained in the same way. They draw attention to the experiments of Cushing and Weed dealing with hypersecretion of spinal fluid following administration of pituitary extracts and suggest that the hormones of the pituitary gland affect the choroid plexus, causing increased secretion of fluid. Amenorrhea, hyperglycemia and hypercholesteremia are explained in a similar fashion. The neprhitic alterations are, according to the authors, secondary to the increased arterial pressure. The authors believe that the hypophysis played a definite rôle in the genesis of the various clinical and pathologic manifestations in their case. NOTKIN, Poughkeepsie, N. Y.

RÔLE OF THE HYPOPHYSIS IN THE TRANSMISSION OF IRRITATION. I. A. DOUBOWIK, Rev. franç. d'endocrinol. **14**:416 (Oct.) 1936.

In a series of previous experiments Doubowik found that irritation of the sympathetic cervical ganglion in frogs inhibits the secretion of the posterior lobe of the pituitary. He found also that stimulation of the stellate ganglion brings about pronounced blanching of the skin in frogs, while extirpation of the ganglia turns the skin permanently dark. Similar experiments carried out with the vagus nerve gave opposite reactions. As hypophysectomized frogs did not show this melanophoric reaction, Doubowik concluded that expansion and contraction of the melanophores are regulated by a melanophoric hormone secreted in the posterior and intermediate parts of the hypophysis. The present work deals with the mechanism of transmission of irritation from the hypophysis to the pigment cells. The experiments were carried out on frogs (Rana temporaria). Epinephrine hydrochloride and bile were used, the latter because it contains choline, which is an antagonist of epinephrine. The changes in the melanophores were studied in preparations freshly cleared with glycerin. Bile was diluted with 3 volumes of Ringer solution. In one series of experiments the pituitary was left intact. Injection of 0.5 cm. of diluted bile into a frog weighing from 25 to 30 Gm. caused weak blanching in from ten to fifteen minutes, reaching its maximum in two hours. Return to normal pigmentation took place in twenty-four hours. Microscopic examination revealed contraction of the melanophores similar to that obtained with epinephrine hydrochloride. For control experiments epinephrine hydrochloride was injected in a series of frogs; this resulted in the classic reaction of Lieben, namely, pronounced contraction of the melanophores after a single dose of 0.5 cm. of a 1 : 1,000 solution of epinephrine hydrochloride.

The second series of experiments was carried out with hypophysectomized frogs. In such preparations a large number of melanophores showed changes in shape, taking on angular forms. When these frogs were given epinephrine hydrochloride no further change in the cells took place. After injections of bile the frogs became inactive, and the skin appeared somewhat darker five or six hours later, retaining this color for the next three or four hours. Microscopic studies of the skin of these frogs showed a change in shape of the cells, which became stellate in the initial stage.

In a third series of experiments the effect of epinephrine hydrochloride and bile on the melanophores was studied after elimination of the influence of the

pituitary body and the nervous system. For this purpose, pieces of skin from the femoral region were inverted in epinephrine and in bile, for six hours. In the epinephrine preparations the cells appeared somewhat stellate, perhaps more pronounced than in the preceding experiment, while in the bile preparations the melanophores became stellate, with processes paler than the cell body.

NOTKIN, Poughkeepsie, N. Y.

RELATION OF THE BASOPHILIC CELLS OF THE NEUROHYPOPHYSIS TO HYPERTENSION AND ECLAMPSIA. K. SCRIBA, Virchows Arch. f. path. Anat. **297**:221, 1936.

A number of writers have ascribed the presence of basophilic cells in the neurohypophysis to invasion from the adenohypophysis and have seen in these misplaced cells the anatomic substrate for nonrenal hypertension and eclampsia. To the basophilic cells of the neurohypophysis is ascribed the property of producing antidiuretic and pressor hormones. Scriba examined serially the neurohypophyses of 346 subjects of both sexes and of all ages, from the fetal period to beyond 80 years. The basophilic cells were observed in fetuses and in children, as well as at all later ages, with no definite increase after the third decade. In general the cells were less numerous in women than in men. The 55 per cent of adults with numerous or fairly numerous basophilic cells were equally divided into those without and those with hypertension. The 45 per cent with few or no basophilic cells were again equally divided into those with and those without hypertension. Scriba therefore concludes that the basophilic cells of the neurohypophysis have no relation to hypertension and that no internal secretory activity can be ascribed to them. In children he observed groups of epithelial cells in the zone intermediate between the anterior and the posterior lobe of the hypophysis. These were derivatives of the posterior wall of Rathke's pouch. In 75 per cent of human beings such cells constitute a rudimentary organ analogous to the pars intermedia of the hypophysis of the lower animals; they have no endocrine function. It is these cells that become transformed into the basophilic cells of the neurohypophysis; the latter is not invaded by basophilic cells from the adenohypophysis.

SCHULTZ, Evanston, Ill. [ARCH. PATH.]

# Society Transactions

## NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

*Joint Meeting, May 4, 1937*

A. A. BRILL, M.D., *Chairman of the Section, in the Chair*

PSYCHOLOGIC INTERRELATION OF THE PHYSICIAN AND THE PATIENT. DR. HERMAN NUNBERG (by invitation).

The first part of the paper is devoted to a discussion of the patient's attitude toward his physician and his illness. The sick person is helpless and in need of protection and care; as a result, he becomes primitive and regresses to the psychic level of childhood. His ego regresses to the earlier stage of development in which he was always sure of being helped and protected. With this change, he adopts an irrational attitude toward the world around him. His relationship to his physician is therefore partially dominated by this regression. He sees in his physician much more than a professional man and considers him, more or less consciously, as omniscient and omnipotent, capable of bringing magic help, just as once, in childhood, he endowed his parents with those qualities. The patient, however, not only admires but fears his physician. It is shown how this aspect of the relationship is connected with the rôle sickness plays in the unconscious of mankind, as a punishment and an expiation—a conception which has existed from ancient times to the present. The physician becomes a kind of priest. This rôle, however, is also included in the child's impression of his parents. The attitude the patient adopts toward his physician is partially a repetition of the attitude he had toward his parents in childhood. The patient's childhood relationship to his parents has, in adult life, been shifted onto the physician. In psychoanalysis such a shift is called transference. The importance of transference is discussed briefly, and it is shown that the physician from time immemorial has unconsciously made extensive use of it.

The importance of transference from the opposite angle, namely, that of the relation of the physician to his patient, is considered in the second part of the paper. Various emotional factors which influence one in becoming a physician and are also active in determining the attitude of the physician to his patient are enlarged on. Some of these factors, in my opinion, are curiosity, repressed aggression, the feeling of guilt and compassion. To clarify and explain to some extent the relationship of the doctor and the patient, I turn to childhood and discuss several varieties of the doctor game which all children play; this gains special significance in the child who later chooses to become a physician. Mainly on the basis of analyses of such doctor games, it is demonstrated what an important part parental identification plays in the physician's choice of his profession. This identification also determines, to a great extent, the physician's attitude toward his patient. He treats his patient in some ways as he himself felt he was being treated by his parents in his childhood—as though the patient represented him as a child and he himself played the part of one or both parents. Thus, one sees that the attitude of the physician toward his patient is likewise greatly influenced by his own childhood, just as that of the patient toward him is determined by the patient's childhood. The patient's transference to his physician and the physician's identification with his own parents, carried over from his childhood into his relationship to his patient, supplement each other. If used consciously and purposefully, transference may become a helpful factor in the process of healing.

DISCUSSION

DR. WILLIAM H. DUNN (by invitation): In discussing Dr. Nunberg's able contribution, I shall utilize material which is drawn from a somewhat different source than his. Any one who works in a general hospital and has the opportunity to observe patients in the psychiatric and in various other clinics is impressed by the patients' attitude of perfect willingness to throw their complete load on the physician in attendance. Most of them present themselves in much the fashion that Dr. Nunberg has described—not only those with organic disease but the great number of persons who come to the hospital presenting physical symptoms but who actually are troubled by some threat in the external environment, due to the severe economic situation to which they are exposed or to some inner conflict. I have the impression that often these patients are set in the belief that the physician is able to dispel all their difficulties, through the medium of physical investigation and treatment, with neglect of the emotional features in the case. After a considerable period the patient is often referred to the psychiatric clinic, and it is interesting to see his reaction to the first interview there. He comes with resentment, which, of course, is a cover for great anxiety. He shows the fear of the physician which Dr. Nunberg has described—the fear of having to expose what he conceives of as his sins and of having to face the reality of the situation in so far as the external environment is concerned. These patients are resistant to the idea of having to face their situation, and one sees that in many the reaction of chronic invalidism develops or that others run to the chiropractor or to the Christian Science healer, looking for magic.

In regard to the physician's side of the situation, discussion of which Dr. Nunberg was not able to complete: Certainly, in considering the mistakes which I have made or in reviewing with other physicians in the clinic situations in which there was conflict, I get the definite impression that the attitude of the physician to the patient was sometimes the forerunner of a therapeutic disaster, or perhaps of something even more serious. Usually the trouble was lack of consistency in attitude. The patient had been permitted to build up the belief that he could depend on the physician for all sorts of situations, and then, for varying reasons, the physician shifted his attitude; in such cases suicidal threat, or sometimes aggressive behavior directed toward the physician may result.

It was my impression that the most important feature of Dr. Nunberg's paper was the stress he placed on the need of the physician's having a good knowledge of himself before attempting to treat certain conditions in the field of psychiatry.

DR. LAWRENCE S. KUBIE: It is a pleasure to discuss Dr. Nunberg's able paper. It is so full of material, however, that it is difficult to decide which points to stress. Perhaps the most significant factor, and at the same time the easiest point to forget is that illness is never a simple reality, either to the patient or to the physician, but an experience which is charged with an extraordinary amount of highly emotional, unconscious fantasies. These fantasies constantly affect the relationship of the patient to his illness, of the patient to the physician, of the physician to his rôle and, often, of the physician to the particular type of illness with which he is dealing. The complexities which enter into the psychologic relationship of persons to disease, whether as patients or as physicians, are endless, and it is impossible to do more than point to them in the few moments at my disposal.

Of these complexities I have never seen a more striking example than that in the case of a sick physician. He would have impressed any one as peculiarly exempt from the danger of neurosis. He was vigorous, successful and happily married; athletics was his chief avocation. There was one peculiar thing: He would never be sick. No matter what was wrong with him, he acted as though sickness were nonsense, the frail foible of weaklings: "My patients may get sick, but I don't." He was almost phobic in his jaunty refusal to take medicine. If he had a cold, he never took acetylsalicylic acid or went to bed. One day, however, he discovered in himself a mild and innocuous metabolic anomaly. This precipitated in him the stored-up panic of a lifetime. He became sleepless, obsessively hypochondriacal and deeply depressed. It became clear that his peculiar attitude

to illness had existed because of what Dr. Nunberg had time merely to mention in passing, to wit, that in greater or lesser degree illness always means the arousal of a peculiar kind of guilt and of anxiety. Between psychoanalysts and their neurologic and psychiatric colleagues there is much discussion about the origin of guilt and anxiety, and one of the things which creates most doubt concerns the psychosexual basis. Fortunately, one can side-step this discussion. For the moment it is enough if all agree that, no matter how anxiety or guilt arises, ultimately they must focus strongly on psychosexual problems. Illness thereon becomes involved in an elaborate system of conscious and unconscious fantasies as the chief punishment for real or fancied psychosexual sins. I cannot discuss all that, but the constant play of anxiety and guilt under the surface of illness demands much greater attention on the part of medical students than it has ever been accorded.

THE FEELING OF STUPIDITY. DR. C. P. OBERNDORF.

The feeling of stupidity, like many other symptoms which can become the predominant complaint in mental disorder, has been experienced from time to time by most persons. It may become disturbing to patients through either the frequency of its occurrence or its intensity. As the symptom is concerned with the process of thinking, it is not surprising that it should have been encountered as the major difficulty in persons suffering from varying degrees of depersonalization and unreality. It is in patients of this type that erotization of thinking, a process also concerned with the value of intelligence, seems to be a critical factor.

The kinship of a disproportionate investment of libido in intellectual precocity and of that in psychogenic stupidity has been noted. In the first type of activity, excessive libido is attached to the processes of thinking; in the second, it appears to be active in the construction of a barrier against the entrance and (or) exit of ideas. The stimulus which seems to determine the mobilization of energy in two such apparently opposite activities depends on the person's choice of identification (superego formation in the sense of Freud) with the intellectual attributes of his parents.

The function of these antithetic activities is similar; each tends to remove the subject from the more real exigencies of life—the one, by the expenditure of too great an amount of libido in study or abstraction, and the other, by establishing a barricade against the entrance or egress of stimuli which might provoke thought or action. When erotization of thought or feelings of stupidity become sufficiently pronounced, they may progress to a sort of mental paralysis which the patient describes as a feeling of unreality.

In previous papers I have advanced the theory that the patient who erotizes thinking has been rebuffed and emotionally traumatized by the stupid parent of the same sex. The case material indicated that such an identification occurs more frequently with girls than with boys and that the person who erotizes thought considers it a characteristic of the opposite sex. A motive which fosters erotization of thinking is that the child considers it to his advantage to use his intelligence as a weapon with which he can combat and humiliate the parent who has deprived him in a libidinal way.

In cases in which the feeling of stupidity has become a major symptom one also finds severe deprivation of love by the parent of the same sex. This parent, however, is considered by the child to be the intellectually inferior one. Instead of attempting to fight this parent by identifying himself with the intellectual parent, the child considers stupidity as the characteristic which has attracted the loved parent. Unconsciously, the feeling of stupidity develops, serving as a reenforcement to the patient's sexual desirability and, at the same time, shutting out the reality of his psychosexual failure.

The object of this presentation is to point out that the feeling of stupidity, like erotization of thinking, serves the function of allowing the patient to withdraw from reality and is associated with disturbance in the feeling of reality. Both depend on identifications which go to make up impulses of the superego, to which I have referred elsewhere as the masculine or the feminine superego. In the

feeling of unreality and of stupidity the manner in which these impulses arrange and exert themselves in superego function depends on the sex of the patient and that of the parent with whose mentality the patient finally identifies himself. When the patient identifies intelligence as a characteristic of the loved parent, he may erotize thinking as a force through which he can humiliate the unloved parent. When he identifies stupidity as a quality by which the unloved attracts the loved parent, the feeling of stupidity serves as a substitute reaction for the affection of the loved parent and, at the same time, as a defense against the reality of his ineffectual rivalry with that parent. The analogy of the two conditions and their close relationship to coconscious thinking, amnesias and dual personality indicate that further investigation of the manner—or the absence—of thinking and feeling may contribute to psychologic understanding of the galaxy of personalities which compose what one calls a person.

DISCUSSION

Dr. James H. Wall, White Plains, N. Y.: The paper of Dr. Oberndorf is interesting. One meets these symptoms in patients suffering from depression, and they are common in states of unreality and perplexity, as pointed out by Dr. Oberndorf in previous papers. It is readily seen to be a manifestation of the spreading inhibition in these conditions. The denial of feeling—the inability to actualize present reality—is closely related to the suppression of instinctive urges incompatible to the person. This is frequently observed in patients complaining of a feeling of stupidity following masturbatory and other sexual activity, in whom there is associated an excessive sense of guilt; here the feeling of stupidity may be equivalent to punishment. It is fascinating to see how this feeling of stupidity has been worked out along the line of identification.

The Social Neurosis. Dr. Paul Schilder.

A group of 18 cases has been studied in which symptoms of social inhibition were in the foreground. The patients showed shyness, inhibition in thinking and of memory, and a tendency to withdraw from social activities. The physical symptoms observed were sweating, blushing, fatigue of the voice and shaking. One may call the condition in this group social neurosis in the narrow sense and consider it as a loose entity among the other groups of related neuroses.

The disturbance is closely related to stammering and erythrophobia. These three types may be called social neurosis in the wider sense.

The fundamental mechanism in cases of this neurosis is an increased tendency to self-love and self-admiration, based on admiration and love given by the parents. The increased demand for self-love and self-admiration can be met only through renewed admiration by others in social contacts; this proves to be insufficient. The social suffering occurs when the person has been pushed also into a passive, masochistic position which needs to be perpetuated in suffering. The pressure may come from the parent of the same or of the opposite sex. The combination of the two will be particularly effective when pressure by aggressive love and strictness are combined.

Anal, homosexual, exhibitionistic and urethral trends may be present. The narcissistic and masochistic attitudes are of paramount importance. The masochistic attitude may be based on dependence on the parent of the opposite sex.

Therapy based on insight into the basic psychologic trends is sufficient. In cases of a severe type psychoanalysis or prolonged group psychotherapy is necessary. Benzedrine is not indicated as treatment for the neurosis but may help in specific situations.

DISCUSSION

Dr. Sándor Lorand: This interesting presentation seems to me to be important for two reasons: first, for the attempted classification of the condition as a social neurosis, and, second, for the clinical material and therapy.

As to the first point: Dr. Schilder does not contend that the condition in these cases must be considered social neurosis because it was produced by the actual

social situation. There is a tendency today to reject the freudian concept and to insist that neuroses are caused by cultural and social situations and that childhood experience—in fact, everything that was formerly looked on as the basis of adult neurotic disturbances—is of no significance. Factors of reality must be considered first of all as causative, and among them one must include social competition, jealousy, feelings of inferiority and aggression. I do not know how generally it is known that Freud has always emphasized that constitution, early experiences, disposition and accidental factors in development and maturity are all interdependent in the causation of neuroses.

It is true that, following Freud, one also considers infantile experiences to be the basis for adult neuroses. It is not hard to understand, however, that the aforementioned factors of competition, feelings of inferiority, jealousy, sibling rivalry and aggression are all present to an even greater degree in childhood.

There is no doubt that economic insecurity may be a precipitating factor in present day neuroses, but the person who succumbs must have had the psychologic weakness from earlier times. In adult life, when these feelings produce neurotic difficulties, one may be certain that the basis of the difficulties was present in the earliest environment. This is why one must trace causative factors to the period of childhood if he would understand the neuroses.

Freud has described cases of social neurosis, particularly in a paper entitled: "Those Who Cannot Endure Success" (Some Character-Types Met with in Psychoanalytic Work, in Collected Papers, London, Hogarth Press, 1924, vol. 4), in which he demonstrated the significance of social factors in the creation of neurotic difficulties. In this particular paper he stressed the importance of external happenings and reality situations. No one denies that daily experiences and social situations can elicit neuroses. I have described such a situation in a paper entitled: "A Case of Social Inferiority" (The Morbid Personality, New York, Alfred A. Knopf, Inc., 1931, chap. 7). One must give close attention to the conflicts caused by actual difficulties and must deal with them daily in analysis. One must know more that that, however, to cure the patient.

Dr. Schilder has stated that even with patients whom he treated by psychotherapy he had to achieve insight into the basic psychologic trends and that he always found that the pressure which brought about the neurosis came from the child-parent situation. For example, he spoke of cases of disappointed vanity in which narcissism played an important rôle in the creation of the difficulties. In going back to the infantile situation, he finds that the neurotic disturbance is based on dependence on the appreciation of the earliest love objects, the parents. The patient's suffering would not be as keenly felt as it is if his anguish did not remind him of the satisfactions derived from masochistic experiences in childhood. As Dr. Schilder put it: "The social surroundings now take the place of the parents."

It is for this reason that I find Dr. Schilder's classification difficult to accept. Although in these cases he calls the disturbance social neurosis, the neurosis has not been caused by the social situation; he gives it this name because the symptoms are mainly those of social inhibition, that is, neurotic symptoms which come to the foreground in social contact. Yet such symptoms may be characteristic of many types of neuroses.

As for the second point, the therapeutic procedure, it deserves consideration partly because the general belief—and the basis for frequent criticism—is that the strictly freudian analysts know only one method, the orthodox analysis, and because to treat a patient strictly *lege artis* means a prolonged analytic process. Here Dr. Schilder, himself an analyst, has cited a number of cases in which, although his basic approach was psychoanalytic and he followed the dynamics of the freudian interpretation, he made use of a varied psychotherapy. Some of his patients were treated for a long period with regular analytic sessions, and others, for a shorter time. Still, he secured good results with the second group, too.

This method of an approach which is not strictly analytic is in fairly common use at present in psychiatric clinics. There may be analysts who doubt the value of such short cuts and in every case of psychoneurosis advocate only what they

would call orthodox analysis in daily sessions. I shall quote briefly what Freud had to say on this question, in a paper written in 1919 and read in Budapest, entitled: "Turnings in the Ways of Psychoanalytic Therapy" (Collected Papers, London, Hogarth Press, 1924, vol. 2, p. 401). Unfortunately, this paper and others in which he discussed the practical aspects of psychoanalysis are somewhat neglected in these days.

"At present we can do nothing in the crowded ranks of the people who suffer exceedingly from neuroses.

"Now let us assume that by some kind of organization we were able to increase our numbers to an extent sufficient for treating large masses of people. Then on the other hand, one may reasonably expect that at some time or other the conscience of the community will awake and admonish it that the poor man has just as much right to help for his mind as he now has to the surgeon's means of saving life; and that the neuroses menace the health of a people no less than tuberculosis, and can be left as little as the latter to the feeble handling of individuals. Then clinic and consultation-departments will be built, to which analytically trained physicians will be appointed, so that the men who would otherwise give way to drink, the women who have nearly succumbed under their burden of privations, the children for whom there is no choice but running wild or neurosis, may be made by analysis able to resist and able to do something in the world. This treatment will be free. It may be a long time before the State regards this as an urgent duty. Present conditions may delay its arrival even longer.

"The task will then arise for us to adapt our technique to the new conditions. I have no doubt that the validity of our psychological assumptions will impress the uneducated too, but we shall need to find the simplest and most natural expression for our theoretical doctrines. We shall probably discover that the poor are even less ready to part with their neuroses than the rich, because the hard life that awaits them when they recover has no attraction and illness in them gives them more claim to the help of others. Possibly we may often only be able to achieve something if we combine aid for the mind with some material support in the manner of the Emperor Joseph. It is very probable, too, that the application of our therapy to numbers will compel us to alloy the pure gold of analysis plentifully with the copper of direct suggestion; and even hypnotic influence might find a place in it again, as it has in the treatment of war-neuroses. But whatever form this psychotherapy for the people may take, whatever the elements out of which it is compounded, its most effective and most important ingredients will assuredly remain those borrowed from strict psychoanalysis which serves no ulterior purpose."

Dr. Simon Rothenberg, Brooklyn: Dr. Schilder's paper on social neurosis is a complete and penetrating contribution to this subject. I wish to remark first on the importance of recognizing and understanding clearly the psychologic foundations of social neurosis because of the ever-increasing number of persons who have become sensitized to the popular and much exploited notions of the inferiority complex. The necessity of differentiating true social neurosis from the so-called inferiority type of anxiety, which frequently is no more than the normal fear of doing something new and of failing, cannot be too much emphasized. I think much harm has been done by the designation of the inferiority complex as a neurotic entity, for it has served too often as a diagnostic haven for many normal defections and inaptitudes or for the lack of persistent application to new tasks.

Dr. Schilder has, I believe, succeeded thoroughly in describing this social neurosis in all its phases and variations and has given a comprehensive interpretation of its dynamic origin. The recognition of this condition, as Dr. Schilder has said, should be limited to a group of symptoms, such as shyness, inability to make contact with other persons and a type of anxiety which manifests itself in such body changes as muscular weakness or shaking, sweating, blushing and difficulty with speech or voice. In the history of these patients one usually finds some particular incident in their lives which they thought initiated the condition and

which may be regarded as traumatic. The description of this type of anxiety could perhaps be likened to the picture of a person who goads himself to bring his personality before a hostile, critical world and whose normal body functions cannot carry out the task. He is thwarted by special inner mechanisms which affect the body and render him incapable of carrying into effect the dictates of his ego. These inhibitions, as well as the symptoms, have been thoroughly portrayed in Dr. Schilder's presentation of cases. It has also appeared to me that this neurosis sometimes precedes and sometimes accompanies other discrete neuroses. This would explain the frequency with which social anxiety is tinged with obsessional, hysterical or paranoid trends.

On the whole, I think one can agree also with Dr. Schilder's theoretical explanations underlying the development of this neurosis. There can be no doubt that it arises from unconscious conflicts over ambivalent feelings toward the parents during infantile life and puberty, when patterns of narcissistic rather than of normal and socially idealistic types are founded. However, I am not altogether persuaded by the thesis that these narcissistic patterns must, of necessity, always take on the passive rôle. Strong exhibitionistic and aggressive trends are traits inculcated and encouraged by parents in early life and may be invested with feelings of anxiety, shyness or fear of ridicule from that time.

Analysis in my own cases has led me to suspect that the fertile ground on which this neurosis grows is the experience of the child during which parental influences cause him to form identifications with the sex character and traits of his parents without necessarily succumbing to sexual inversion. Self-appreciation early, as well as later, in life is largely described in terms of masculine or of feminine valuations. "A strong big boy" or "a nice little girl" has less moral and social implication in the narcissism of children than have the innate sex traits. This supposition is borne out further by analysis in several cases of social anxiety in women in which they revealed the awareness in themselves of masculine appearance or trends of action. One of my women patients, who was otherwise fairly well adjusted, could not come before any group without suffering anxiety. This anxiety was connected with the fear that people would notice the appearance of her nose and that her hats were unbecoming. Analysis showed that these ideas referred to puberty, when she was forced into aggressive situations by an older brother who dominated her after her father's death and, at the same time, ridiculed her for her gawkiness and masculine appearance. In the woman whose case Dr. Schilder described one also can see that her anxiety and shyness arose from her resistance to the need of conforming to her father's expectations. He expected her to be aggressive rather than passive—a substitute for his wish for a son. Her inability to be in the company of women likewise pointed to a consciously charged masculine rôle which she could not endure. The high demand for her art and life, together with her father's wishes for aggressiveness, should have caused her to feel complacent in the aggressive rôle, since this was the pattern of the original demand of both parents. Nevertheless, her urge was toward self-castration and masochism. It seems to me that her normal narcissistic investment was on the side of her feminine passive identification, probably with her mother, who also had made demands of perfection on her. The hybrid development of personality from the homogeneous influences of both parents can never be equal and usually results in a leaning toward greater identification with one than with the other sex character. I believe that most of the symptoms of this neurosis spring from the constant awareness of and resistance to sexual identification with the opposite sex. Fear that the outside world will recognize that the behavior in either the upper or the lower level of life is not altogether pure in type is the cause of this social neurosis. It is for this reason also that the suffering takes place only when the patient is in contact with people, and not intrapsychically, as in other neuroses. The ability of the patient to tell incidents in which he first suffered loss of self-estimation or narcissistic failure can be considered not as the fundamental cause but only as the emergence of the neurosis. Such incidents can be traced easily as having symbolic reference to more significant and determining

elements of the neurosis. I, too, have noted the frequent association of shyness with sweating and have been able to trace this to embarrassments and fear of loss of bladder control. This fear usually resulted in the symptom of frequency in urination.

I wish to add a few words on the question of therapy. I have no experience with Dr. Schilder's interesting and novel group therapy. However, I may say that my experience with the orthodox method of analysis in these cases has taught me that there is a danger in treatment which must be avoided, that is, permitting the analysis to drift into intellectualization. Even the theoretical discussions of interpretation of symptoms cause the patients to seize on the opportunity for rationalizing and thereby escaping from the situation of transference. Whatever aggressiveness they possess is largely relegated to the intellectual sphere, and hence they wish to find satisfaction in the exercise of this urge instead of in social and pleasureful activities. In my experience, only through the constant working out of transference situations was I able to obtain permanent results. However, the good results obtained by Dr. Schilder with his new approach surely cannot be disregarded and should be pursued further, in order to find more corroboration and wider meaning for psychotherapy, which up to the present has been only meagerly understood.

THE TRANSFERENCE PHENOMENON IN A CASE OF PHOBIA. DR. FRITZ WITTELS.

DISCUSSION

DR. J. H. W. VAN OPHUIJSEN (by invitation): Dr. Wittels' clear presentation of a case of anxiety hysteria has undoubtedly created a vivid picture of the patient and his behavior during analytic treatment. It would be an easy task for me as an analyst to point out many details which Dr. Wittels mentioned and which could be used in support of the freudian theory concerning the importance of transference in treatment. On the other hand, I should also be able to express differences of opinion on certain points in this presentation, especially in regard to the way in which the transference situation was handled by Dr. Wittels. However, I prefer to undertake the more difficult task of looking at the material presented by Dr. Wittels from the standpoint of a person who does not believe in psychoanalysis and who is opposed to it, in order to bring out the weak points in Dr. Wittels' presentation. I am sure that he knows of these weak points and that he will appreciate this way of discussing his paper, for it will enable him to answer some of the objections which are constantly being made by those who are not acquainted with psychoanalysis.

Dr. Wittels gave the history of a man aged 26 who suffers from the conditioned form of anxiety called a phobia. The patient has a phobia for being alone. It is not known of what he is afraid—whether of something which may happen to him from the outside when alone or of something he may do to himself. There is some indication that the second supposition is the right one. On one occasion, namely, when Dr. Wittels left him to another analyst, he expressed the fear of jumping out of the window. This is scanty material indeed. I can only add that the patient has neither fear nor anxiety in the presence of his mother. Nothing is known about the development of this anxiety in the patient. It is known only that he grew up in an environment in which there was disharmony between the parents; he must have lived under tension, in difficult outward circumstances, and certain conflicts must have developed. One obtains the impression that the mother greatly infantilized her son and that the father, who left the family and remarried, must have been a disagreeable person in the original family setting. Speaking descriptively, one might say that a certain type of pattern was bound to develop in the patient. He had acquired the habit, one might say, of avoiding all situations which seemed difficult or dangerous, and he had carried over the infantile attitude of seeking refuge in the presence of his mother. As the first instance of transference in analysis, or, rather, before the analysis started, Dr. Wittels cited the behavior of the patient when he consulted him for the first time. From the

standpoint of a nonanalyst it is not clear why this case should be one of transference. It is not simply another instance in which the patient showed his symptom of anxiety? There is no material to prove that he was trying to find his father, whom he loved, when he looked into the doctor's room. In fact, there is no proof that he really loved his father, except, perhaps, a dream cited by Dr. Wittels. I shall return to that dream later. His behavior in the waiting-room before he entered Dr. Wittels' office, was simply a repetition of his ordinary manner, and there is no reason to find an explanation by introducing the element of transference. The analyst as such, the man he did not know, was an unknown danger to him, and it was natural for one in whom this pattern had developed to run back to a person with whom he had always found refuge, and so enter the new situation in the company of his mother. That he decided to continue the treatment and stay with Dr. Wittels is readily explained by the fact that he was suffering from his neurosis and expected a cure through treatment by the analyst. It also seems that there is need of much more material than has been given in Dr. Wittels' paper, in order to accept his explanation of the patient's fear—that some one was listening at the door—as a case of transference. In fact, one would be inclined rather to suspect quite another symptom—the expression of a pathologic suspiciousness, even though that would not be in harmony with the clinical picture. On the other hand, I must say that if one accepts the theory of transference in this case, it is not clear why Dr. Wittels should have opened the door to show the patient that there was no one listening behind the door. The nonanalyst might have done it, but from the standpoint of the analyst who accepts the transference theory, this seems the wrong method. Dr. Wittels knew the suspicion was not well founded; by opening the door and thus treating the suspicion as having possibly a real basis, he excluded, it seems to me, the possibility of analyzing the patient's suspicion. Had he not opened the door, the patient would have been forced to speak of his suspicions and to give the reasons that he thought his father's second wife was listening at the door. The same objection holds good in some other instances of transference which Dr. Wittels has cited, but time does not permit me to mention these.

There are a few other points which I am sure a nonanalyst would consider as well known generalizations and as hasty conclusions of the analysts. I was especially struck by an instance to which I referred before. After a discussion about paying the fee, the patient had the following dream, which had a direct connection with the conversation: "I was in bed with my father, and he tried to rape me. In this dream I felt like a woman, afraid and affectionate at the same time." Dr. Wittels stated that this dream is clearly one of the castration type. Of course, I do not know what knowledge of analysis one may take for granted in a meeting like this, but I am sure that those who are opposed to analysis would say at this moment that there is no indication of castration. On the contrary, the son felt, as he expressed it, like a woman, afraid and affectionate at the same time. Why not consider that dream as an expression of homosexual attachment of the son to his father?

The material which was added later, namely, the recollection of the father killing an animal which attacked him, is said to furnish the proof that the dream was an expression of a castration complex. However, it could be easily interpreted in terms of the patient's fear, of his anxiety, the father evidently being the personification of that which he feared—the terrible man who was able to kill the animal, or any other being, who attacked him.

These are the points I wished to mention with regard to Dr. Wittels' interesting presentation, and my object, of course, is not to belittle what Dr. Wittels has given; for as an analyst I am conscious of the truth of his statements and the correctness of his interpretation of certain symbols. I wish, by discussing the material from the standpoint of a nonanalyst, to warn that interpretations made as quickly as those in this paper must be bewildering and must make a wrong impression on persons who are not in the habit of looking at neurotic material from the analyst's point of view.

## CHICAGO NEUROLOGICAL SOCIETY

*Annual Meeting, May 20, 1937*

FRANCIS J. GERTY, M.D., *President, in the Chair*

CHRONIC TETANUS (PRESENTATION OF PATIENT). DR. DOUGLAS N. BUCHANAN.

E. C., a boy aged 6½ years, was admitted to the University of Chicago Clinics on April 17, 1937. He was the elder of two children, born by normal delivery after a normal pregnancy. His early development was normal, and he had never had any serious illness or accident. In April 1936 he returned from a visit to the country, apparently in perfect health. The first night after his return he awoke and complained of severe pain in his teeth and gums. He was taken to a dentist, who made a diagnosis of tetanus, and the child was admitted to a hospital in Gary, Ind. In the hospital there rapidly developed the signs and symptoms of acute tetanus, and he was treated for this disease. He was fed with a tube for four weeks and was given tetanus antitoxin; he was discharged eight weeks later. He had then improved to such an extent that he could swallow but was still unable to open his mouth fully or to speak distinctly. During the next three months, which he spent in the country, he remained stiff in all his muscles and continued to have difficulty in swallowing and speaking.

In January 1937 the muscles became stiffer than before; his speech became almost unintelligible; he fell frequently and had an unsteady gait. He was kept in bed during March.

On examination the boy is cooperative but apprehensive. He seems normally intelligent for his years. His facial appearance is unusual for a child, with a constant frown, a transverse smile and constant tension in the platysma muscle. When walking he shows high dorsal kyphosis and strong muscular development of the entire body; all movements are so stiffly performed that he looks like an old man with stiffness in all joints. He runs slowly and very awkwardly, with no speed. In speaking he keeps his lips closed, and all the muscles of the throat and neck are tightened into spasm. He can feed himself and swallow, but these movements are slow and labored. When he looks to one side he turns his head and trunk together.

The cranial nerves are normal. Each fundus shows a normal disk, with no evidence of swelling, atrophy or hemorrhage. Both pupils are 3 mm. in diameter; they react to direct light through a good range, and the reaction is rapid and well held. There is no limitation of external conjugate movement in any direction, no nystagmus, no strabismus and no ptosis. There is a true transverse smile, with a wrinkle in the forehead. The tongue can be protruded with difficulty and through only a small range. The deep reflexes are all present and are symmetrical and brisk. The superficial reflexes are all present and normal. There is no weakness in any limb and no alteration in the appreciation of sensory stimuli in any part of the body. The patient shows no ataxia, but rapidly alternating movements cannot be performed. The gait is not ataxic, but he walks slowly and stiffly.

*Laboratory Findings.*—The Wassermann and Kahn reactions of the blood were negative, and examination of the blood and urine gave normal results. The spinal fluid was clear and colorless, with an initial pressure of 180 mm. of water, normal dynamic reactions, normal chemical constituents and 6 mononuclear cells per cubic millimeter. The Wassermann reaction of the spinal fluid was negative. The calcium content of the blood was 9.4 mm. per hundred cubic centimeters, and the phosphorus content, 4.9 mm. Cultures of the blood and the spinal fluid produced no growth. Culture of the stools showed tetanus bacilli in large numbers. Roentgenographic examination showed that the skull, chest, pelvis, long bones and epiphysial development were normal.

The impression is gained that the disease is chronic tetanus.

SCOLIOSIS WITH TUMOR OF THE SPINAL CORD. DR. ERIC OLDBERG.

The history of a case of extreme scoliosis of the spine is presented in which subsequent neurologic symptoms were responsible for laminectomy. A large intramedullary tumor of the spinal cord was disclosed. The association of tumor of the spinal cord and scoliosis is discussed, and the opinion is expressed that the scoliosis which results in cases of this sort is like that which occur in growing persons in association with other diseases of the spinal cord, such as syringomyelia and anterior poliomyelitis. A differentiation was made between this condition and that obtaining in Scheuermann-Schmorl's disease, in which neurologic symptoms occur because of herniation of the nucleus pulposus and the spinal deformity is an antecedent rather than a resultant condition.

DISCUSSION

DR. R. P. MACKAY: I am glad that Dr. Oldberg has brought up the subject of scoliosis because some confusion about it exists. In such cases as that which he has reported one observes two series of phenomena; one osseous maldevelopment, and the other, an intramedullary tumor. A similar association is frequent between scoliosis and syringomyelia. It is often assumed, as by Dr. Oldberg, that the scoliosis results from the intramedullary process by virtue of paralyses which produce disturbance in the mechanical pull of muscles on the spinal column. Although scoliosis may occur in poliomyelitis, I doubt whether this explanation holds good in cases of intramedullary tumor and syringomyelia.

DR. PAUL C. BUCY: I believe that Dr. Oldberg and I are essentially in agreement on this subject. I wish to make clear one point. I agree that the condition in the spinal column in his case is not Scheuermann's disease (kyphosis dorsalis juvenilis). On the other hand, I am convinced from the study of cases in the clinic, as well as those reported in the literature, that the vertebral changes associated with a spinal extradural cyst are identical with those of Scheuermann's disease. The picture differs from that shown here. It is interesting that only 10 cases of extradural cyst are on record. Of those, 9 occurred in adolescents and 1 in an adult. In all 9 cases there were associated disturbances of the vertebrae which were typical of those which Scheuermann described in the various stages of kyphosis juvenilis. The first alteration seen is notching of the anterior corners of the vertebral bodies; then herniation of the intervertebral disks into the substance of the body occurs, and the vertebra collapses, giving rise to the kyphosis. The involvement is never sufficient to permit complete collapse of the body, and the result is round kyphosis. In the adult such changes were not present. I believe that these changes occur only in the growing vertebral bodies of adolescents and are the result of interference with the venous drainage from the vertebral bodies by pressure of the extradural cyst.

One cannot conclude that in every case kyphosis dorsalis juvenilis is associated with an extradural cyst. But in cases in which there is such an association I believe that the cyst is responsible for the kyphosis and not that the kyphosis is responsible for the cyst. In cases such as Sachs and McKenzie described, in which paraplegia developed about puberty in a person with severe scoliosis which had begun early in childhood, an entirely different situation obtains. In these cases the scoliosis developed as the result of congenital deformity, rickets or poliomyelitis. In these instances the paraplegia resulted from the severe scoliosis. At the apex of the lateral curve one finds the spinal cord compressed between the convex bony wall of the spinal canal, on one side, and the tautly stretched dura mater, on the other. Section of the dura mater to relieve this compression will result in alleviation of the paraplegia in many instances. Obviously Dr. Oldberg's case does not belong either to the last group or to the cases of spinal extradural cyst associated with kyphosis dorsalis juvenilis.

DR. BEN W. LICHTENSTEIN: Several months ago I reported at a meeting of the Chicago Pathological Society the clinicopathologic study in a case not unlike that presented by Dr. Oldberg this evening. It was that of a white man aged 20

who entered the hospital complaining of urinary disturbances of one and a half years' duration. Since the age of 3 years this man had had a deformity of the back, and during these years the kyphoscoliosis progressively increased in severity. In the months prior to his admission to the hospital there had developed difficulty in gait. Neurologic examination revealed, in addition to the marked dextro-kyphoscoliosis in the thoracic region, paraplegia in flexion of both lower extremities with sensory disturbances up to the nipple line. At necropsy a centrally placed intramedullary tumor of the spinal cord was observed, which proved histologically to be a ganglioglioneuroma. The tumor was centrally cystic and had destroyed the majority of the anterior horn cells in the thoracic portion of the spinal cord. It is my belief that the kyphoscoliosis was the result of the tumor, which had been growing progressively since the age of 3 years. There was no evidence of dystrophia in the spinal cord.

DR. MEYER SOLOMON: Recently, in looking over the volume entitled "Diagnostic Roentgenology" in "Nelson's Loose-Leaf System," I found a chapter by Dr. C. G. Dyke, on roentgenographic findings in association with tumor of the spinal cord; in it is a small section on scoliosis and kyphosis. As I recall, Dyke's view, based on many cases of tumor of the spinal cord in which the diagnosis was verified by observations at operation or autopsy, was that in cases of such a tumor associated with scoliosis or kyphosis the deformity is merely a coincidence. Even when present, it is not helpful in localizing the site of the tumor. He emphasized, as Camp and others have done, the observation of deformity in the pedicles and increase of the interpedicular space. I wonder whether search was made for changes in the pedicles and what the findings were and whether there were any differences in the interpedicular spaces, for which Dyke gives the range of normal variations.

PARS NERVOSA OF THE HYPOPHYSIS. DR. CHARLES FISHER (by invitation).

During the past five years an extensive investigation of the mammalian hypothalamus has been carried out at the Institute of Neurology at the Northwestern University Medical School. One of the main results of this work is the light that has been thrown on the structure and function of the neural lobe of the hypophysis. I wish to present a brief summary of these researches, which were carried out in collaboration with Dr. S. W. Ranson and Dr. W. R. Ingram.

The neural lobe of the hypophysis, which consists of three parts, namely, the median eminence, the infundibular stem and the pars nervosa, is innervated by the hypothalamicohypophysial tract. This tract is made up of two components: the supra-opticohypophysial tract, which arises from the anterior portion of the hypothalamus and chiefly from the supra-optic nuclei, and the tuberohypophysial tract, the fibers of which arise from neurons in the lateral and caudal peri-infundibular areas. All three parts of the neural lobe appear to have the same histologic structure. The chief histologic elements are the unmyelinated nerve fibers, the modified glia cells known as pituicytes, the endothelial cells of the capillaries, the mast cells described by Gray, a rich capillary plexus and a stroma of connective tissue. Bilateral lesions in the hypothalamus of the cat or monkey placed with the Horsley-Clarke stereotaxic instrument so as to interrupt the supra-opticohypophysial tract bilaterally produce regularly diabetes insipidus. To date, we have produced this disorder in 85 cats. When these tracts are interrupted a series of striking degenerative changes is produced in the neural lobe of the hypophysis and in the hypothalamus. The supra-optic nuclei show marked atrophy and nearly complete disappearance of cells. All three parts of the neural lobe become thin, atrophic and hypercellular. It has been demonstrated that the unmyelinated nerve fibers degenerate and can no longer be seen in the neural lobe after interruption of the hypothalamicohypophysial tract. The pituicytes likewise appear to have degenerated. Within the first two weeks after operation the neural lobe and its central cavity are filled with phagocytes, but in the chronic condition these cells are no longer present and are replaced by an element not yet identified. The changes in the monkey are identical with those in the cat.

It has been concluded that diabetes insipidus is due to deficiency in the antidiuretic hormone normally secreted by the neural lobe. The disorder arises when this lobe undergoes the sort of atrophy just described and also after its extirpation. In extirpation experiments it has been found that the neural lobe must be removed in its entirety, including the median eminence and infundibular stem, if diabetes insipidus of any proportion is to develop. Atrophy of the neural lobe is not a fortuitous circumstance. We have demonstrated that the atrophic neural lobe in these experiments is markedly deficient in antidiuretic activity when subjected to appropriate assay. The normal neural lobe of the cat contains from 7.5 to 10 antidiuretic units, while the atrophic gland contains no more than a few tenths of a unit.

The question of the site of formation of the so-called hormones of the posterior lobe is discussed. It is concluded, on the basis of our work and that of Geiling, that the neural lobe itself, independent of the pars intermedia, elaborates these hormones.

The possibility that atrophy or extirpation of the neural lobe produces another deficiency symptom is briefly discussed. It is pointed out that a number of the diabetic cats in our series which were operated on at various stages of gestation were able to carry their litters to term but showed a striking disturbance in the mechanism of delivery. It is suggested that this disturbance may be related to the deficiency of the atrophic neural lobe not only in antidiuretic and pressor but in oxytocic activity.

Finally, it is concluded that, from the point of view of antidiuretic function at least, the neural lobe of the hypophysis is an endocrine gland, for: (1) its atrophy or extirpation leads to a deficiency syndrome, namely, diabetes insipidus; (2) the atrophic gland is deficient in antidiuretic hormone; (3) the deficiency syndrome can be relieved by substitution therapy, namely, injection of extracts of the neural lobe containing the antidiuretic hormone, and (4) extracts of the posterior lobe contain the antidiuretic hormone, and the evidence indicates that this hormone is elaborated by the tissue of the neural lobe and not by the pars intermedia.

DISCUSSION

DR. PERCIVAL BAILEY: I wish to know how Dr. Fisher explains the results of Mahoney and Sheehan (*Brain* **59**:61, 1936). There are many things about diabetes insipidus which I am unable to explain satisfactorily to myself. My associates and I in the clinic at the University of Chicago know that often after intense polyuria a patient will return to a normal urinary output, although the lesion is progressive and continues to a fatal termination. This leads me to ask if in any of the cats the diabetes disappeared, although at necropsy the lobe was observed to be atrophied, and, if so, how this was explained.

DR. S. W. RANSON: In recent years there have appeared in the literature a number of papers which fit in well with the work that has been reported by Dr. Fisher. Richter, at Johns Hopkins University, and Pencharz, at the University of California, have produced diabetes insipidus by removal of the posterior lobe of the hypophysis. In England, Biggart has reported a number of cases of diabetes insipidus in man in which there was damage to the supra-optic nucleus and the pars nervosa of the hypophysis. Quite recent, and so far reported only before the American Physiological Society, is the work by Dr. C. C. Hare, at Cornell University, which showed that removal of the pars nervosa in the dog is followed by marked atrophy of the supra-optic nucleus. The work of Gagel and Mahoney (*Ztschr. f. d. ges. Neurol. u. Psychiat.* **156**:594, 1936) on the monkey has not been repeated, but when we made lesions in the hypothalamus, interrupting the supra-opticohypophysial tract, we obtained the same results in the monkey as in the cat, namely, atrophy of the supra-optic nucleus and the pars nervosa of the hypophysis. In reply to the question raised by Dr. Bailey: It is my opinion that the reason that Gagel and Mahoney did not produce changes in the supra-optic nuclei in their experiments was that they failed to interrupt the tract.

DR. CHARLES FISHER: In reply to Dr. Bailey's question about the failure of Mahoney and Sheehan to produce diabetes insipidus in the monkey by placing

clips on the infundibular stem, I may point out: Mahoney and Sheehan stated specifically that they placed the clips as low as possible on the infundibular stem, and hence they could well have left significant remnants of the stem and median eminence. We have shown that such remnants can prevent the appearance of diabetes insipidus. The neural lobe, like all other endocrine glands, has a large factor of safety, and it appears that a small portion of it can, within certain limits, carry the function of the whole.

Dr. Ranson is, I believe, correct in assuming that Mahoney and Sheehan failed to section the infundibular stem or, at best, succeeded in interrupting a small fraction of the fibers of the hypothalamicohypophysial tract. They reported that there was only slight atrophy of the supra-optic nuclei and neural lobe. We have observed that when the hypothalamicohypophysial tract is interrupted by lesions of the hypothalamus, these structures show marked atrophy. We have not sectioned the infundibular stem in the monkey; so we have no direct evidence of our own that this procedure produces the same sort of atrophy in this species, although we have shown that it does in the cat. However, there is a little known piece of work which was reported by Morawski (*Ztschr. f. d. ges. Neurol. u. Psychiat.* **7**:207, 1911), in which it was shown that section of the stem results in atrophy of the neural lobe in the monkey. Morawski reproduced several photographs showing the same sort of atrophy of the pars nervosa as I have discussed tonight. I am persuaded, therefore, that if Mahoney and Sheehan interrupted the hypothalamicohypophysial tract at all, they secured only slight and partial interruption.

With reference to Dr. Bailey's second question: I can state that we have never observed the spontaneous disappearance of marked diabetes insipidus in the cat, provided that the animal remained in good health and continued to consume its full ration of food. We have found, however, that if the animal becomes ill (acquires an infection of the respiratory tract, distemper or the like), the polyuria and polydipsia may disappear during the illness and return after the animal recovers. Sometimes such illness may result in the permanent disappearance of mild diabetes insipidus. Clinically, it has been reported that diabetes insipidus caused by a tumor of the posterior lobe may disappear if the tumor spreads to involve the anterior lobe. Such cases have been interpreted as evidence for the von Hann theory, to which we subscribe, which holds that diabetes insipidus develops when the supra-opticohypophysial antidiuretic mechanism is destroyed, provided sufficient tissue of the pars anterior is present to maintain the animal in a fairly normal state of metabolism and activity.

SPEECH PRODUCTION OF TWO PRESCHOOL CHILDREN: REFERENCES TO SEX ORGANS AND SEXUAL FUNCTIONS; A QUANTITATIVE STUDY. DR. A. A. LOW.

This paper will be published in full in a later issue of the ARCHIVES.

IN MEMORIAM—WILLIAM G. STEARNS.

Dr. Stearns was first of all a cultured gentleman—kindly, tactful and possessed of infinite patience. These traits explain his success in the home treatment of neurotic and psychotic patients. He was a master in selecting suitable nurses and vocational and recreational activities for his patients. He found time to listen to and talk with them for hours every day for months, and even years. He also treated many patients in the North Shore Health Resort during the past thirty years and was the medical superintendent of that institution for several years before his death in January 1937.

He was born near Fond du Lac, Wis., in 1865. At the age of 17 he was 6 feet tall, but in poor health; so he had to interrupt his education and spent several years in South Dakota—part of the time as telegraph operator at a small station. He then attended the State Normal School at Oshkosh, Wis., the normal school at Potsdam, N. Y., and the Chicago Medical College (now the Northwestern University Medical School), where he graduated in 1893. His roommate while at the medical school was the late Dr. Frank T. Stevens, of Colorado Springs. After an internship in St. Luke's Hospital, Stearns became pathologist and assistant

physician at the Kankakee State Hospital and was its superintendent from 1897 to 1899. During his sojourn at Kankakee he found time to serve as professor of pathology at the Northwestern University Dental School. For several years he was professor of nervous and mental diseases at the Northwestern University Medical School. A detailed outline of his course in psychiatry was printed in the university bulletin. While at Kankakee, he formulated an elaborate outline for history taking and the examination of patients, which gives a good picture of the psychiatric concepts of the time, dominated by the degeneration theories of Lombroso and Nordau, with emphasis on anthropologic measurements. This outline was copied by many institutions in other states. From 1901 to 1905 Stearns was superintendent of the Lake Geneva Sanitarium, but maintained an office in Chicago. He was vice president of the Chicago Neurological Society in 1920 and 1927 and was a member of the American Psychiatric Association and the Central Neuropsychiatric Association.

Stearns was of old American stock. His first American ancestor, Isaac Stearns, missed the "Mayflower" by only ten years and landed at Salem Harbor in 1630, together with Governor Winthrop, from the ship "Arabella." In a book on the Stearns family (Van Wagenen, Avis Stearns: Genealogy and Memoirs of Charles and Nathaniel Stearns and Their Descendants, Syracuse, N. Y., 1901, vol. 2, p. 35) one reads: "There is a traditional anecdote of the first landing of the Stearns family as follows: that on reaching anchorage Isaac, like the spies sent into Canaan, went forward and selected a place of settlement. Soon after an emulation arose between the two boys [nephews of Isaac] as to which should step on the land first, and as they sprang from the boat, Charles Stearns missed his footing and fell into the river, which was thereafter christened the Charles River." Nevertheless, the historian claims for the name a royal origin.

## PHILADELPHIA NEUROLOGICAL SOCIETY

*Regular Meeting, May 28, 1937*

J. W. McConnell, M.D., *President, in the Chair*

A Case of Isolated Homonymous Hemianopia. Dr. Samuel B. Hadden.

J. C., a white man aged 41, a detective in the city police department, was admitted to the Philadelphia General Hospital, in the service of Dr. Hubley R. Owen, on April 6, 1936. His chief complaint was headache and loss of vision in the right eye, of ten days' duration. Ten days before admission the patient experienced flickering of lights before the right eye, with constant pain over the left eye and loss of memory for recent events. The flickering lights appeared to the right every four or five minutes and lasted for several minutes. He gradually became aware of failure of vision on the right. He became confused and did not feel confident in finding his accustomed route.

Physical examination revealed a plethoric, obese man, with flushed face. The pupils were normal. There were no extra-ocular palsies. Apparently, there was right homonymous hemianopia. Examination of the eye grounds showed slight filling of the physiologic cup. The blood pressure was 118 systolic and 78 diastolic. No other findings of importance were noted.

On the following day I observed the patient in attacks during which he became confused and there was conjugate deviation of the head and eyes to the right. These attacks occurred at intervals of about fifteen minutes and lasted a minute. They were preceded and followed by a period of confusion of from one to two minutes. At this time there was no disturbance of the tendon reflexes nor any sensory disturbances. Since the only finding was complete homonymous hemianopia, the diagnosis of thrombosis of the left posterior cerebral artery was made, with the possibility of tumor of the left occipitoparietal region to be ruled out.

Four days after admission the patient had a series of convulsions lasting approximately six hours, during which there was conjugate deviation to the right. Convulsive movement appeared in the upper and then the lower part of the face, the right arm eventually becoming involved in the convulsion. The right leg remained tonic. After several attacks the patient became unconscious and he did not regain consciousness until the following day, when definite paralysis of the right side of the face and right hand was noted. This disappeared the next day, and on the fourth day following the convulsive seizures the patient was about in a wheel-chair.

He was discharged on May 1, when his only symptoms were hemianopia and anomia, which developed after the convulsive seizures.

The significant laboratory findings at this time were blood sugar levels during fasting of 217, 189, 178, 200, 170 and 120 mg. per hundred cubic centimeters. A blood count showed a hemoglobin content of 104 per cent and 6,250,000 red cells. The Wassermann reaction of the spinal fluid was negative.

The patient was readmitted and studied from December 1 to December 30. Hemianopia was complete. There was slight weakness of the right side of the face of the central type. The anomia had improved considerably, but on excitement there was mild motor aphasia. At no time since discharge had the patient experienced headache, and there was no swelling of the optic nerve. On December 2 an encephalogram revealed no distortion of the ventricular system. After encephalography there developed more marked motor aphasia and slight sensory aphasia, which have persisted, or possibly increased, to the time of reporting.

At present the findings are: right hemianopia; complete, slight weakness of the right side of the face of the central type with anomia, and definite motor and sensory aphasia. There is no apraxia, but when the patient is given objects and told to demonstrate their use he is slow in doing so. Although at all previous examinations there was no disturbance in naming objects, he identified them by stereognostic means but could not name the object when it was shown to him. He now has difficulty in identifying such objects. The blood count at present shows a hemoglobin content of almost 100 per cent and 5,860,000 red cells.

This case is presented as one of possible occlusion of the posterior cerebral artery, which, I believe, occurs far more frequently than occlusion of the posterior inferior cerebellar or anterior spinal arteries and is not nearly so well known.

ABSCESS OF THE BRAIN OF UNDETERMINED ETIOLOGY: REPORT OF 4 CASES IN WHICH RECOVERY OCCURRED. DRS. J. C. YASKIN, F. C. GRANT and R. A. GROFF.

Diagnosis of abscess of the brain implies the determination of etiologic factors. The abscess may be due to direct extension or hematogenous spread, or the source of the infection may be doubtful or unknown.

Four cases of solitary cerebral abscess of undetermined etiology are reported. All the patients recovered after operation. In 2 cases the abscess was so thickly encapsulated that it was removed at operation in the belief that it was a tumor.

From the study of these cases, the opinion is submitted that the combined occurrence of severe, especially unilateral, headaches, persistent slow pulse and evidences of increased intracranial pressure should suggest, even in absence of evidences of infection in the nervous system or elsewhere in the body, existence of an abscess of the brain. Timely diagnosis is indispensable in the surgical treatment of cerebral abscess.

DISCUSSION

DR. F. C. GRANT: I take exception to the statement of Dr. Yaskin that one must be careful in differentiating between tumor and abscess of the brain because the surgical attack on these two lesions is diametrically different. In neither of the 2 cases in which I operated, that of the girl and that of the man, who is not present, was it believed that there was an abscess of the brain until I cut into the

lesion and found that it was not a tumor but a thickly encapsulated abscess; in both cases the abscess was removed exactly as though it were a tumor. That was nothing but sheer luck. It was fortunate indeed that the abscesses were so well encapsulated that they were susceptible to removal. I have found it feasible to give the abscess a chance to form and coalesce and then to shell out the whole mass. I think that the handling of an abscess depends a great deal on luck. I believe it makes no difference how or when one operates, whether one taps or drains the abscess or cuts away the cortex; if the abscess is encapsulated one can do almost anything with it. For that reason, I think that if one waits one can better carry the patient through, without fatality.

DR. R. A. GROFF: I wish to make a clinical observation in the third case, in which I was fortunate enough to carry the patient through. This man had a history of symptoms of one week's duration. When the abscess was unavoidably tapped, there was no capsule. The rupture of the abscess through the cortex was plugged, and about two days later the plug was removed. This gave me an opportunity to study the development of the capsule. Ten or fourteen days after operation one could see the capsule forming; it was beginning to show consistency. If one takes this period of fourteen days and adds seven days during which preoperative symptoms appeared, it would seem three weeks were required for the capsule of the abscess to form. I think this interesting clinical observation indicates that if the patient's condition warrants, one should wait about three weeks before encapsulation of the abscess can be anticipated.

DR. ROSS THOMPSON: I wish to ask Dr. Grant if, in his experience, he has ever known an abscess of the brain to recur after successful operation. I was interested in the case of a boy in whom a large abscess was successfully drained, with complete recovery and discharge from the hospital. In three months he returned to the hospital with symptoms indicating return of the abscess in the identical situation. It developed so quickly that there was not sufficient time to wait for encapsulation, and he died during exploratory operation.

DR. WILLIAM DUANE JR.: I wish to add something to corroborate what has been said. The case of the girl reported reminds me of 2 cases I have seen in the last month. In the first the condition was fulminating, and the spinal fluid showed various organisms. The patient died. In the second case the abscess appeared four weeks after extraction of teeth, which provided the focus of infection. The patient is now in the hospital, and I have tapped the abscess five times. There are still organisms in the pus, and the abscess keeps reforming. In this case there is a tremendously thickened capsule. If I had suspected an abscess in the first place, I think I should have operated. In both cases the abscess was in the frontal lobe.

DR. TEMPLE FAY: I think that Dr. Grant's emphasis on when to attack the lesion is probably the crux of the matter, particularly in infections of this type some of which become encapsulated. From the historical standpoint, it is extremely interesting to know that Ambroise Paré in 1568 reported a series of cases of abscess of the brain in which there was remarkably low mortality. His method of dealing with these abscesses was the same as that described here. He awaited localization. The patients with a diffuse, nonencapsulating infection died then, as they do now. Judicious delay of operation followed by decompression over the lesion, allowing migration to the surface, was practiced then, as Dr. Edgar Kahn advocates now.

Ambroise Paré believed in first opening the scalp and trephining the skull and three days later opening the dura mater, allowing the brain to bulge forth. Then he introduced lead tubes into the capsule of the abscess.

Another point for which I admire him: Each day in dressing the patient he advised him to hold his nose and strain, thereby pushing the pus out. Is this not the best way to increase intracranial pressure! It seems one still can go back to the old masters. I can recall when an abscess was considered an emergency in

which operation was to be performed immediately after the diagnosis was made. Now I believe that if one can wait for a capsule to form the best results can be obtained.

DR. B. J. ALPERS: I hesitate to inject a spirit of skepticism into this consideration, but I wish to point out that the problem being discussed here is that of chronic abscess of the brain. These abscesses are encapsulated. However, in cases of acute abscess there is an acute surgical problem and it is fatal to wait for encapsulation. Such abscesses occur with sinus disease and must be dealt with promptly. Furthermore, I question whether one can reduce the problem of the surgical treatment of abscess to the simple denomination of encapsulation. There are abscesses of the brain which encapsulate imperfectly, or not at all. Must one not take into account the virulence of the organism, the resistance of the host, the presence or absence of infections of the blood stream and other similar factors?

DR. J. C. YASKIN: It will be noted that our neurosurgical colleagues confine their remarks to the necessity of waiting for encapsulation of the abscess prior to operation. They seem to imply that the diagnosis of abscess of the brain is a relatively simple procedure. In practice this is frequently difficult, even if a source of possible infection is present or suspected. In the absence of any infection diagnosis of the abscess is often impossible. In the first case reported here there was doubt as to the existence of any space-taking intracranial lesion. In the second case the preoperative diagnosis was tumor. In the first 2 cases the abscess was removed *en masse,* in the belief that it was a tumor. In the third case we suspected an abscess but knew, because of the short duration of the illness, that it would not be encapsulated; yet we could not risk delay in the operation. In the fourth no delay could be considered, irrespective of encapsulation. In view of the experiences mentioned, it would seem that suspicion of the existence of an abscess of the brain in the absence of infection may be aided by the criteria submitted in this presentation.

AIR MYELOGRAPHY IN THE DIAGNOSIS OF LESIONS OF THE SPINAL CANAL, WITH SPECIAL REFERENCE TO THOSE OF THE NUCLEUS PULPOSUS AND TO THE "SCIATIC SYNDROME." DRS. MICHAEL SCOTT and BARTON R. YOUNG (by invitation).

Since January 1936 air myelography has been used as a routine procedure at the Temple University Hospital by the departments of neurology and neurosurgery, in conjunction with the department of radiology. No claim is made for originality in using air to outline the spinal canal, but we believe that we were among the first to demonstrate herniations of the nucleus pulposus by its use.

This report is based on 10 cases of lesions of the spinal canal in which the level of the block was found by air myelography and confirmed by laminectomy. In 6 of the cases there was a tumor, and in 4, a herniation of the nucleus pulposus. In one of the cases a diagnosis of "sciatica" had been made. Ober's fasciotomy and section of the pyriformis muscle had been done previously, without relief of pain. Laminectomy, performed by Dr. Temple Fay, revealed herniation of the nucleus pulposus at the level of the fifth lumbar lamina. The method of injection of air and the roentgen technic are discussed and five air myelograms shown.

We conclude that the use of iodized poppy-seed oil is not justified in outlining the lumbocaudal sac or in finding the level of a complete block in any part of the spinal canal. This can be done with ease and without complications by the use of air myelography. The entire spinal canal in case of an incomplete block can be outlined by placing the patient in the Trendelenburg position and through cisternal puncture replacing the spinal fluid with air until air returns from the needle.

The dangers in making a final diagnosis of idiopathic "sciatica" should be emphasized, and it is suggested that in all cases in which no organic basis is found the lumbocaudal sac be outlined by air, in order to rule out a tumor or lesion of the nucleus pulposus.

DISSEMINATED ENCEPHALOMYELITIS: A HISTOLOGIC SYNDROME ASSOCIATED WITH THROMBOSIS OF SMALL CEREBRAL VESSELS. TRACY J. PUTNAM, Boston (by invitation).

The possible relationship between the occurrence of thrombosis of small cerebral vessels and the lesions of "encephalomyelitis" and multiple sclerosis has been considered in previous papers. The present paper is devoted to a study of the thrombi which were observed in all cases of "encephalomyelitis" studied, in 3 of which the disease followed vaccinia, in 3 measles, in 2 rabies, in 1 tonsillitis, in 1 exposure to carbon monoxide and in 1 exposure to nitrogen monoxide; in 3 the disease was of similar type but of unknown etiology. Thrombi were also observed in similar lesions in a case of encephalitis (encephalitis B) occurring in the St. Louis epidemic and in 1 apparently of the type (lethargic encephalitis) described by von Economo.

Since thrombi are seen constantly in connection with this characteristic histologic reaction, since the reaction occurs wherever appropriate vascular occlusion of whatever origin is present and since it may be produced experimentally by various measures which interfere in certain ways with the cerebral circulation, there appears to be reason to believe that the vascular occlusion is primary and not secondary to the parenchymal changes. If an infectious agent is present also in the lesions, evidence of its existence must be sought by other than histologic means—for example, in fulfilling Koch's postulates.

DISCUSSION

DR. N. W. WINKELMAN: I wish to place myself on record as commending Dr. Putnam for having so ably attacked a problem that has been one of the most baffling in the domain of neurology. His presentation this evening is part of a concerted attack on a problem which must have bearing on many related conditions, including encephalomyelitis disseminata, acute multiple sclerosis and multiple sclerosis. Dr. Putnam has given a classification of the encephalitides. It differs in many essentials from those of former authors but in the main fits in with the general principles outlined by them.

Pette, for example, divided the encephalitides into two main groups: (1) those attacking by preference the gray matter and (2) those preferring the white matter. In the former he included polio-encephalitis, von Economo's disease (lethargic encephalitis) and experimental herpes encephalitis. In the second group he included the postvaccinal type of encephalitis, acute disseminated encephalomyelitis and acute multiple sclerosis.

The classification that Spatz used differs in many essentials from that given by Pette. For discussion here I need mention only the fifth and sixth groups. His fifth group comprises acute disseminated demyelinizing encephalitis, including epidemic encephalitis and multiple sclerosis, and his sixth, acute perivenous encephalitis. His distinction between these two subdivisions was that in the perivenous type there is a known antecedent systemic infection.

The conception that Hassin has given is in better agreement with the histopathologic than with the clinical or experimental differentiation. He divided the entire group into the types resulting from degeneration and those from inflammation. The first type is represented, according to Hassin, by postvaccinal encephalitis, while the inflammatory type is represented by encephalitis associated with measles. He expressed the belief that acute multiple sclerosis, acute disseminated encephalomyelitis and the classic form of multiple sclerosis cannot be considered as one disease process.

Globus took an intermediate view between the opinion expressed by Dr. Putnam this evening and the stand taken by Hassin.

Dr. Putnam this evening has shown concrete evidences of thrombi in the veins, with areas of demyelinization in the immediate vicinity. This has not been the observation of previous authors, probably because staining methods used by them have not been as accurate as those employed by Dr. Putnam. It is likely that

with the Masson stain or with similar stains others will see thrombotic lesions in the veins more frequently than they have in the past. In previous work Dr. Putnam has shown that venous thrombi can result from various factors. If the mechanism of the condition is definitely determined and the factors producing the condition can be known, one is nearer a solution of the problem than in the past.

DR. B. J. ALPERS: This is a lucid presentation, and I wish to add my word of appreciation. First, for the sake of argument, I grant that there are venous thromboses in these lesions. I think this is necessary in order to arrive at a reasonable discussion of the problem. I am all the more willing to grant this because in the slide which I sent Dr. Putnam these thromboses could not be seen with stains used as a routine but were demonstrated by Dr. Putnam on special examination.

The first problem I shall discuss is the relation to multiple sclerosis of the lesions which Dr. Putnam has demonstrated. Are all types of disseminated encephalomyelitis the same? In my estimation, they differ from multiple sclerosis in the life histories, since the end-result of a patch of multiple sclerosis is gliosis and scar, whereas in lesions of the type which Dr. Putnam has demonstrated this has not, I believe, been conclusively shown. I agree with Dr. Putnam that one cannot insist too strongly on the criterion of preservation of axis-cylinders in the differentiation of lesions. Axis-cylinders may be intact, in general, in plaques of multiple sclerosis; in old plaques, however, many of them may be destroyed, and a similar situation may hold for disseminated encephalomyelitis.

The relationship of plaques to the vessels is clear in many instances, but it has been my impression that this is much more definite in cases of perivenous encephalomyelitis than in those of multiple sclerosis. However, one cannot be too dogmatic about this matter without a study of serial sections in these cases.

Finally, I wish to state that it is my belief that the patchy type of encephalomyelitis is different from the perivenous type.

This is true not only by virtue of the pathologic characteristics but from a clinical standpoint. For purposes of comparison, it is probably wise to emphasize the similarity in this group of diseases, but I think that one cannot disregard the fact that the differences are still more marked. Some may be minor, but disregard of these minor differences may lead one far astray from the true solution of the problem.

DR. M. A. BURNS: I shall discuss Dr. Putnam's paper from the clinical standpoint. Every time that the question is raised whether multiple sclerosis is endogenous or exogenous, inflammatory or degenerative, one is reminded that our New York colleagues have discussed this condition from time to time without coming to any definite conclusion. If one is at least clinically to distinguish encephalomyelitis disseminata and acute multiple sclerosis, Dr. Putnam has opened up a tremendous avenue of thought as to the differentiation of these conditions. However, from the point of view of the theory that venous thrombosis occurs in encephalomyelitis disseminata and Dr. Putnam's observation that in acute multiple sclerosis there is also distinct venous thrombosis, there must be a definite association between these two conditions, and one is encountering conclusive evidence which may be accepted in the near future.

DR. SAMUEL HADDEN: I feel much more comfortable after Dr. Alper's statement that even neuropathologists are not in agreement on what constitutes multiple sclerosis and encephalomyelitis disseminata. One must agree with Dr. Putnam's conception that multiple sclerosis does not constitute an etiologic entity. I believe that one of the factors which confuses the histopathology of this condition is that the lesions are seen and described by different observers in different stages. What is seen in a particular specimen depends considerably on the time at which it is observed in relationship to the onset. The thrombotic lesions which Dr. Putnam observed are not generally recognized, possibly owing to inadequate staining methods. Since in much of Dr. Putnam's work he has controlled the period between the production of lesions and their histopathologic study, I wish to ask

if he is able to confirm the observations of Dr. Penfield in relation to the time required for glial reaction to occur in the nervous system.

DR. T. J. PUTNAM: There is considerable variation in the thrombi present in "encephalomyelitis" and multiple sclerosis. The earliest change seems sometimes to be agglutination of platelets and sometimes precipitation of fibrin. Endothelial changes occur only in the later stages. Finally, necrosis of the wall or closure of the lumen to form a fibrous cord may be observed.

The thrombotic changes are reminiscent of those produced by Shwartzman by repeated injections of bacterial filtrates. Dr. Shwartzman let me have some of his material, and my associates and I produced with them mild chronic lesions in 1 of 5 animals. I believe that some of the processes leading to instability of the plasma may come under the head of allergy.

I believe, as Dr. Burns does, that many etiologic factors may produce multiple sclerosis which have only a final mechanism in common.

In regard to the time factor, it takes from two to four months for fibrous gliosis to develop in animals, and it grows denser as time goes on. The development was more rapid in Penfield's experiments, doubtless because the insult was more intense.

Dr. Alpers and Dr. Winkelman have raised the question of classification of the encephalitides. The classification which I have offered is crude but practical, the purpose of which is to encourage search for similarities rather than for differences. In my experience, the perivenous type represents an early stage of what may later develop into patchy encephalitis. Thus, Cramer and Schlesinger each reported cases of postmeasles encephalitis in which the histories were typical and the picture of multiple sclerosis was presented at autopsy several months later. In Habermeier's case of postvaccinal encephalitis in which death occurred late, an obvious vascular lesion was present, which he disregarded in his conclusions.

I believe that the more acute the process the more marked the destruction of axis cylinders. The most exquisite demyelinization with preservation of axis-cylinders which I have ever seen was observed in an animal subjected to experimental obstruction of cerebral venules.

In regard to the constancy of occurrence of thrombi: I have observed them in all the cases of "encephalomyelitis" of this type (12 up to the present) in which I have had sufficient material to cut several blocks. Only thin paraffin sections of formaldehyde-fixed material stained by the Masson technic or of material fixed in Zenker's solution and stained by the Mallory connective tissue method are satisfactory for study. Most neuropathologic technics are especially designed to neglect the blood vessels.

# Book Reviews

**Vom Sinn der Sinne.** By Erwin Straus. Paper. Price, 12 marks. Pp. 314, no illustrations. Berlin: Julius Springer, 1935.

The book is written from a broad point of view. The title might have been "Philosophy Underlying the Chief Schools of Psychology and Their Criticisms." The work is divided into three parts. The first two are concerned almost entirely with evaluations of the teaching of conditioned reflexes. The third deals with the theories of James, Ebbinghaus, Klages, Katz, Werner, Foerster and the gestalt school of Koehler and the relation of these theories to the philosophy of Descartes in particular and also to that of Berkeley, Bain and Aristotle.

Straus deals not with specific experiments or the details of any of the schools but with the underlying theories and implications. Written from a wide perspective and based on knowledge of and insight into the subject, the book is essentially a criticism and comparison of all the schools. Although the emphasis is on the errors inherent in the underlying philosophies, the discussion is not altogether negative, as the author leaves one with the sense of the relative importance and background of the schools.

Modern psychology is based on the cartesian teaching of perception. Descartes' definition of consciousness is: *"Alles, was so in uns ist, dass wir es unmittelbar durch uns selbst bemerken, auch davon eine innere Erkenntnis haben."* His views of body and mind are given. Straus says that the cartesian philosophy concerning perception underlies the whole teaching of the psychology of the nineteenth and twentieth centuries; therefore one must go back to Descartes. James, however, introduced the idea of "transitive parts" in addition to the "substantive parts" of the stream of consciousness. The discoveries of Pavlov were a later fulfilment of the cartesian philosophy.

Pages 26 to 82 are concerned with a direct criticism of the teaching of conditioned reflexes. The author prefaces this, however, with a comparison of Pavlov and Columbus, who while not finding what he set out to discover, made, nevertheless, a great contribution. *"Eine Kritik an Pawlow muss darum eine positive Kritik sein."* Of the three possible subjects of criticism in Pavlov's work (the accuracy of his results; the equivalence of his experiments to simple *Dressur* and their insignificance therefore for natural life, and the underlying theories), it is only the theories that the author considers deserve criticism.

The unique position of Pavlov arises from the fact that he was "famous before he was known," on account of the enormous accumulation of material which was thrown at once, instead of piecemeal, on the world. Pavlov's followers, reasoning that his observations were purely objective, simple and comprehensible, assume that the theories arise directly from the results of the experiments and that these results prove the theories. On a universal atomistic significance of such phenomena as distance, changes and direction is built Pavlov's physiology. "All physiologies of the central nervous system of man are hypothetical, but Pavlov's exceeds all others in the number of unproved hypotheses."

Pavlov considered himself objective when he spoke in physical terms; he attempted to translate sensation into a language not of sensation but of physics, by which Straus thinks that much is lost.

The difficulties in accepting Pavlov's theories are as follows: The orienting reflex cannot be considered as the response of a physical machine, for it is related only to a new situation whereas a machine reacts to every identical situation equally. (The machine built by C. L. Hull to illustrate the formation and inhibition of conditioned reflexes would controvert this argument.) Straus considers that the Pavlovian conception of the trace reflex plus irradiation leads to a reductio ad absurdum. Pavlov did not explain the phenomenon of emptiness.

In the second part of the book the author undertakes to explain Pavlov's facts and observations, which he admits are real. Instead of the signal's being of a

dual nature, the symbol of the signal should be written I to S to D, in which I indicates the indifferent situation, S the signal and D the different situation; i. e., the signal is a transition from the indifferent to the different situation. The author proceeds to discuss the significance of the signal and the problems of the known and the unknown, of the "between," the general and the special and of emptiness.

The third part of the book deals with perception and self-movement considered historically. "Perception is thus a sympathetic experience," but the author does not mean that it is the expression of a universal harmony. The unity and the multiplicity of the senses are discussed versus the cartesian teaching of senseless perception, as well as epicritic and protopathic sensitivity. For Descartes and Berkeley sensations are beyond the spirit.

In discussing the relation between the teachings of Katz, Werner and O. Foerster, it is stated that Foerster said that with the affective system of deep sensitivity there is an anatomic and a physiologic perceptive epicritic system. Foerster's concept of inhibition is purely physiologic.

In treating the dependence of sensation and movement it is stated that physiologic psychology considers all movement as reflex and that on several reflexes are built instinctive and voluntary movements, making reflex and voluntary movement the same. This is a fundamental error, however, for the subject of reflex movement is the muscle or the *sensomotorium* while that of mental movement is the animal or the human being. The muscle is set in motion; the man moves himself. This is an expression of Adolf Meyer's concept of the whole versus the part. The cartesian error lies in considering physics as the basis of psychology. Straus refers to the falsity of the physical point of view by which movement is considered as a process in the organism rather than as a situation involving the organism in space. A nerve and a muscle cannot stand in the relationship of totality. The movements of dancing are impossible to interpret from the physical point of view.

For James and Ebbinghaus voluntary and automatic movements are only a repetition of reflex movements, resting on charged motor nerve cells. From the author's point of view, however, movement is definite; it is referred to the totality of experience and has a certain order. It proceeds according to an inner system and is not, as James thought, simple repetition of accidental movements. When the author states that the unmusical cannot learn to sing and play the piano, he is giving another version to the principle that interest and emotion are usually necessary for habit formation. Automatic movement is thus not a separate movement with an absolute beginning and an absolute end, from A to B., but a movement from a "here" to a "there." It thus has all the marks of self-movement.

The author finds no salvation in the gestalt psychology of Koehler. In comparing landscape with geography, noise with music and the animal with the human family, one finds proof that the human world of reality is radically different from the animal world of sensation.

Several pages are devoted to a discussion of the problems of time and space. Psychiatry is touched on: Hallucinations arise not from disturbance in the physiologic sensorium, not from impaired function of the perception of reality but from an aberration of the sympathetic function of sensation.

The author shows insight into his subject-matter. The book is written in an easy, clear and inoffensive style. It has no index but probably does not need one, as it is intended to be read through rather than to be used for reference.

**Ueber die Erkennung der traumatischen Hirnverletzung.** By E. Grunthal. Cloth. Price, 14.80 marks. Pp. 116, with 17 illustrations. Berlin: S. Karger, 1936.

In the preface of this book the author emphasizes that the syndromes resulting from minor accidental injuries of the brain are inadequately known; he believes it instructive, therefore, to point out errors in diagnosis in seventeen cases in which the

injury to the brain was not recognized clinically. The value of his cases lies in the long clinical observation and anatomic verification. The nature of the trauma was a blow in ten cases, a fall in six and crushing in one. Fracture of the skull was present in thirteen cases—the result of a blow in eight, of a fall in four and of a crushing injury in one. In three instances roentgenograms showed nothing abnormal. The lesion was located in the frontal area in thirteen cases, in the parietal in two and in the temporal in one. In eleven instances the injury to the brain was related to the site of trauma and in five was distant from it. The following errors in diagnosis are pointed out: In three cases hysteria was falsely taken for epilepsy; in four cases the mental syndrome was not recognized as organic, and in six instances actual hysterical manifestations were present, diverting attention from the organic background.

Immediate posttraumatic symptoms are of importance. Unconsciousness occurred in nine cases. In others symptoms appeared after varying intervals. In eight cases in which there was not immediate loss of consciousness, a confused state or mental dulness was present, lasting for several hours or weeks. In the past this condition has been diagnosed as postconcussional psychosis, but in the author's opinion it is a sign of severe injury to the brain. In nine cases permanent psychic changes could be demonstrated: excitability, irritability, intolerance to alcohol, confused state, dulness, lack of initiative and slowness and disturbance in thought processes. The first three disturbances are general symptoms following any injury to the brain; the others the author relates to a lesion of the upper posterior part of the frontal lobe. After a lesion of the orbital region (in one case) release of instinctive inhibition and leveling of the emotional state were seen. Lesions of the white matter seem important. As is frequently noted in lesions so situated, epilepsy and long-standing mental changes developed in cases of this injury. Subjective disturbances are dominated by headache, dizziness, insomnia, hypersensitiveness to noise, fatigability and the subjective feeling of difficulty in thinking. The symptoms may be latent for a long time, especially in young patients, and relatively slight trauma may provoke them. It is not correct to speak of reactive hysteria in such cases. Finally, the intelligence, the character and the circumstances of life are also of importance, for they may influence the symptoms.

The second part of the monograph deals with the disturbance in thought processes (*Denkstörung*) following a lesion of the frontal lobe. It is characteristic of this syndrome that ordinary sensorial perception is practically unimpaired, but as soon as the patient faces a task demanding active thought, an active concentration of attention, the greatest difficulty appears and the patient is subjectively aware of lack of thought. The necessity of dealing with concrete—as opposed to abstract—subjects, difficulty in simple enumeration, disturbance in estimation of time, peculiar behavior toward colors, loss of individual ideas and fragmentation of thought action, all can be traced to the same basal disturbance, i. e., hindrance of each inner willed act of experiencing (*"eine Behinderung jedes inneren aktiven Erlebens"*).

The author renders a service in calling attention to often neglected injuries of the brain and in pointing out that they are often erroneously diagnosed. However, in some instances (cases 9, 11, 12 and 13) it seems to the reviewer that the small focal lesions held responsible for psychic disturbance might better be regarded merely as indicators of a more general injury to the brain to which insufficient study has been given. The analysis of the disturbance in thought processes following lesion of the frontal lobe is logical and instructive.

**Psychogenic Tonsillitis.** By Rudolf Bilz, Zentralbl. f. Psychotherap. (Supp.) **9**:1, 1936.

The subtitle of this pamphlet states that it deals with the psychotherapy of tonsillitis. Bilz gives the history of a government official aged 35 who was suddenly taken ill with tonsillitis before his engagement was announced. During the illness the prospective engagement was broken off. The author studied intensively

the dreams and associations of the patient and demonstrates how the illness was an expression of unconscious conflicts between homosexual and heterosexual tendencies. The psychologic material brought out during the course of the disease demonstrates the struggle and the final abandonment of the masculine rôle of a father and husband. The material brings out also the patient's fantasies of pregnancy, so that the pharynx becomes a symbol of the patient's genital apparatus by a process of displacement. Combined with this is a strong element of self-punishment.

Bilz compares the illness of his patient with the strange custom of couvade in some primitive races, in which after his wife's parturition the man goes to bed for a few days. Couvade, according to Reik, represents psychologically the expiation act on the part of the father for the aggressive tendencies toward the new-born child. In this case there seems to be a close resemblance between the patient's illness and a fear of the responsibilities of manhood, with self-punishment expressing itself in the symptoms, fantasies and dreams of the patient. Although the parallel appears to be justified and there is a fascinating presentation of the phylogenetic material, it seems to the reviewer that certain of the mechanisms would be clearer if actual analysis of the patient had been undertaken. The author makes an interesting point in trying to find an organic basis for the symptoms of anxiety. He postulates that there must be a chemical substance in the body which counteracts anxiety and which serves as an antagonist to epinephrine. He points to the recent contributions concerning acetylcholine and lymphoganglin (a hypothetical hormone from lymph glands). He postulates a theory according to which the lymphatic tissue has the effect of neutralizing anxiety. When the anxiety is very strong, much of the defensive apparatus of the lymphatic system is spent in neutralizing this anxiety, so that the defensive forces of the organs are depleted and infection takes place more readily. This explains the tonsillitis in this and in other cases.

The author presents interesting, if somewhat speculative, psychopathologic considerations with reference to problems of infection, especially tonsillitis, which merit further investigation. The language, unfortunately, is ponderous and heavy, making it difficult to follow some of the ideas.

**Handbuch der Neurologie.** Edited by O. Bumke and O. Foerster. Volume V. General Symptomatology III. Spinal Cord, Brain Stem and Cerebellum. Price, 128 marks. Pp. 639, with 345 illustrations. Berlin, Julius Springer, 1936.

This volume in the now famous "Handbuch" of Bumke and Foerster is one of the finest yet to appear in the series. It has an extensive monograph by Foerster on the symptomatology of diseases of the spinal cord, which is a strikingly fine work. It contains not only excellent clinical discussions but a discussion of physiologic and clinical subjects of great value to neurologists. This particular discussion on the spinal cord is an outstanding contribution. F. Lotmar contributes a useful chapter on the general symptomatology of the basal ganglia, and Környey also has a good chapter on the medulla, pons, midbrain and corpora quadrigemina. There is an excellent chapter on the symptomatology of diseases of the hypothalamus by Gagel, which contains much useful information on a subject to which contributions are being made constantly. Stenvers contributes a chapter on the postural reflexes. This not only is well done but supplies a real need, since a concise discussion of the clinical meaning of these reflexes is difficult to find elsewhere. Finally, there is a chapter by Marburg on the diseases of the cerebellum.

The volume as a whole is one of the best in the series. Like all the other volumes which have appeared, it is well printed and illustrated and is enthusiastically recommended to neurologists.

**Handbuch der Neurologie.** Edited by O. Bumke and O. Foerster. Volume VIII. General Neurology VIII. General Therapy. Price, 131 marks. Pp. 749, with 182 illustrations. Berlin, Julius Springer, 1936.

This volume contains chapters on pharmacotherapy of the nervous system by A. Fröhlich, which is an excellent review of the various means at command for treatment of the nervous system by means of drugs. There is an excellent chapter by J. Wagner-Jauregg on fever therapy in syphilis of the central nervous system, multiple sclerosis and other nervous diseases. W. Lehmann contributes a long and valuable article on the surgical therapy for diseases and injuries of the nervous system. There are also a good article on orthopedic treatment of paralyses by G. Hohmann and a good chapter by O. Foerster on physical therapy in cases of peripheral and central lesions of various sorts. There is a long and comprehensive chapter on electrotherapy by L. Mann and one on the roentgen treatment of nervous diseases by O. Marburg and M. Sgalitzer. This includes a comprehensive discussion on treatment of various nervous diseases by means of radiation. A. Strasser contributes a chapter on hydrotherapy; E. Wexburg, one on balneotherapy and climatotherapy, and J. Reinhold, one on psychotherapy.

The volume covers in detailed fashion all aspects of treatment of the nervous system. It is excellently done, well illustrated and fully up to the standard of the previous volumes in this series. It combines in a single volume many matters in relation to treatment which would be difficult, if not impossible, to find elsewhere. The book can be highly recommended to all neurologists and will serve as a valuable volume for orientation concerning the treatment of diseases of the nervous system.

**The Ocular Fundus in Diagnosis and Treatment.** By Donald T. Atkinson, M.D., F.A.C.S. Price, $10. Pp. 259, with 106 engravings, including 58 colored plates. Philadelphia: Lea & Febiger, 1937.

This is a monograph on the fundoscopic findings in health and disease. There are numerous illustrations, over half of which are colored plates—all illustrations being by the author himself. While the plates are of some interest, the text which accompanies them indicates very little understanding of the neurologist's problem in examining the fundi. For example, the subject of choked disk and its relation to increased intracranial pressure, which is discussed together with numerous other causes of "papillitis," is dismissed with a few words, among which may be found statements such as: "Tumors of the brain, inflammatory conditions of the brain or of its meninges, tumors within the orbit, chronic sinusitis, pregnancy, epilepsy, or alcoholism may be complicated by choked disk. . . . When occurring coincident with meningitis or brain tumors, it is nearly always unilateral." "In papillitis due to increased intracranial pressure, the condition has sometimes been benefited by trephining the skull and by spinal puncture." The book is not recommended for purchase by neurologists.